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TABLE *of* CONTENTS

SPECIAL ARTICLES

The Ever-Continuing Search for Immunity in Tuberculosis.
J. ARTHUR MYERS, M.D. 101

Management of Breech Presentation.
ALLAN C. BARNES, M.D. 124

Herpes Zoster.
PEARCE BAILEY, M.D. 127

Frigidity in Women.
J. P. GREENHILL, M.D. 145

Cumulative Effects of X-Ray Exposures.
PAUL C. HODGES, M.D. 152

Some Practical Aspects of Lumbar Puncture.
RAYMOND F. COURTIN, M.D. 157

Medical Examination of Prostitutes.
CHARLES W. CLARKE, M.D. 162

DIAGNOSTIC CLINICS

Surgical Intrathoracic Cardiovascular Lesions.
JOHN W. KIRKLIN, M.D. 118

Acute and Chronic Osteomyelitis.
ROBERT M. O'BRIEN, M.D. 133

Duodenal and Gastric Ulcer.
SAMUEL F. MARSHALL, M.D. 137

GENERAL PRACTICE REVIEW

Current Use of Antibiotics.
WILLIAM E. WELLMAN, M.D. 167

SCIENTIFIC EXHIBIT

Congenital Laryngeal Stridor.
A. C. STUTSMAN, M.D. 174

(Continued on page A-6)

PEDIATRICS IN GENERAL PRACTICE

Foot Problems in Children.
DOUGLAS T. LINDSAY, M.D. 177

DEPARTMENTS

EDITORIALS 181

When He Comes Ashore
The Use of Virus in Human Cancer
More Trouble with British National Health Service
Pharmacology in Medical Progress

MEN OF MEDICINE. *Elise Strang L'Esperance, M.D.* 186

LEAVES FROM A DOCTOR'S DIARY. Maurice Chideckel, M.D. A-20

YOUR QUESTIONS ANSWERED A-26

Treatment of Inguinal Wound
Sudden Onset of Fainting and Vomiting
Bilateral Cryptorchism in Newborn Infant
Reduction of Fehling's Solution

REPORTS FROM ABROAD A-34

THE EDITOR'S MAIL A-40

THE MEDICAL BOOKMAN A-50

NEW DRUGS AND INSTRUMENTS A-59

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-84

INDEX TO TECHNICAL EXHIBITS A-100

THE 1952 Assembly *OF THE*

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of North America

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The Ever-Continuing Search for Immunity in Tuberculosis

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In this first section of a three part article, the author offers an historical sketch of early attempts to produce immunity against tuberculosis artificially. Live tubercle bacilli reduced in virulence, as well as those killed by various methods, were employed to produce immunity by numerous world renowned workers, including Koch, Von Behring and Calmette. A large number of such "immunizing agents" was developed. Calmette and Guérin used living tubercle bacillus isolated from a tuberculous cow in 1902. After reducing its virulence they named it Bacillus Calmette-Guérin (BCG) and strongly recommended its administration to both animals and humans.

J. A. MYERS

THERE is reason to fear that one of the most dangerous health travesties in history is now in operation with reference to tuberculosis. Of all diseases in the world, tuberculosis still causes more incapacity and death among human beings and domestic animals than does any other. During the twentieth century, methods of combating this disease have been developed which have proved so effective that in some places eradication is now envisioned. These methods are so fundamental, yet so simple, that they can be employed any place in the world where people have the will to eradicate tuberculosis. Wherever they have been in operation sufficiently long, the tuberculosis problem has been reduced to a mere shadow of its former self. Indeed, there are areas where this disease has been completely eradicated from school children.

These fundamental methods of tuberculosis control are now being seriously threatened by a theoretical procedure of unproved efficacy with a probable harmful effect. This procedure consists of introducing into the human body large numbers of live tubercle bacilli called BCG (*Bacillus Calmette-Guérin*), on the theory that their presence results in immunity or resistance to virulent tubercle bacilli if and when they later invade tissues.

The propaganda now employed to convince the public and even professional health workers of the harmlessness and efficacy of living BCG goes far beyond any justifiable level. This propaganda stems mainly from a few physicians who

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direct or are associated with laboratories which produce BCG in Europe and in Central, South and North America. These physicians, who are excellent laboratorians and are well informed on the tubercle bacillus as it behaves in the laboratory, have become overzealous concerning the ability of BCG to control tuberculosis in man and animals. Assertions have been so extreme as to attract and convince a sizeable number of followers who have accepted statements as facts and have demanded no well documented evidence of harmlessness or efficacy. In some places, "vaccination" with BCG has been made compulsory for certain groups of people. Physicians who have refused to administer it or to have it employed in their own families have been referred to as ignorant or uncooperative individuals who are denying people this *one* opportunity to be protected against tuberculosis. Persons who refuse these living tubercle bacilli in mass "vaccination" campaigns have been designated "timid souls."

In speaking of the period between the discovery of the tubercle bacillus and the year 1913, Von Ruck[1] said: "These antigens have multiplied to such an extent that even a concise description of their preparation and claimed advantages would easily fill a small volume."

In 1927 Schroeder[2] said that the reports on attempts to immunize against tuberculosis since the tubercle bacillus was discovered would fill several large volumes and would present the names of many famous investigators.

Wilson[3] says: "Vaccination with BCG is now so universally applauded that any attempt to question its value is regarded almost as heresy."

Andrews,[4] following an extensive tour, wrote a summary of past activities as well as those in progress with BCG, and pointed out that never before in medical history has so much work been done on such slender evidence and with such a woefully incomplete knowledge of the substance being used.

Attempts have been made to reach every person through newspapers, magazines, radio broadcasts, etc., with many assertions which have no factual bases. Misleading statements—such as, "We vaccinate against smallpox, why not against tuberculosis?" "A new method," "A recently discovered tuberculosis preventive," etc.—have been made with such definiteness and finality that even a few physicians with great reputations in other phases of medicine have nodded approval and allowed their names to be used in support of a method of which they have taken little cognizance.

Such propaganda is threatening to destroy in large part the program of tuberculosis control developed over the decades by the medical profession and its allies, including great organizations, particularly the National Tuberculosis Association. Already, persons with contagious tuberculosis who previously have been content to be isolated in hospitals and sanatoriums are becoming insistent on returning to their homes, and those in homes are opposing admission to institutions because they believe their children and other associates can be effectively vaccinated against tuberculosis.

It is said that some legislators have become less liberal toward making appropriations for building sanatoriums or even for repairing and providing adequate maintenance for those already in operation because they have been convinced that BCG will render such institutions obsolete in the next few years. People are wondering about the advisability of buying tuberculosis Christmas Seals, since they believe the work they support will soon be unnecessary because of vaccination.

Laymen have written personal letters, spoken from platforms, etc., in the promotion of BCG. Physicians have been approached and reprehended by such persons. One received a letter with reference to tar and feathers for his part in opposing BCG. Another layman, in a letter referring to the opposition of some medical men to widespread use of BCG, said the explanation most often voiced is: "With the immediate reduction and the eventual elimination of TB as a major disease, many medical practitioners and TB sanatorium operators and directors will find their lucrative sources of income seriously curtailed—hence the violent opposition on the part of some to any program having as its objective the virtual elimination of TB." This statement is being made despite the fact that physicians in tuberculosis work have long been known to be among individuals in the medical profession with the lowest incomes.

This propaganda, including solicitation, legislation, threats, intimidation and much more, has led to considerable confusion among physicians, especially the 90,000 general practitioners in this country. They have a tremendous responsibility in the tuberculosis eradication program which, to date, they have discharged in a magnificent way. Inasmuch as severe criticism is being leveled at the segments of the medical and veterinary professions as well as at their allies who cling to safe and efficacious methods of fighting tuberculosis, and because the most successful eradication program of all time is so endangered, it is imperative that results of studies on immunity be presented from the time of Koch's announcement to the present.

Early Attempts to Produce Immunity Artificially

Soon after Koch published his paper (1882) it seemed to him and to others that an artificial immunizing agent would soon be available. This already had been done for smallpox, fowl cholera and to some degree for anthrax. However, such an agent had not been produced for the acid-fast bacillus of leprosy discovered by Hansen in 1874. A number of physicians and scientists, including Koch, set to work to devise methods of weakening the tubercle bacillus or raising resistance of animals to it. The first attempt was made by Falk,[5] who treated animals by inoculation of tuberculous tissue, by which method he hoped to weaken tubercle bacilli by putrefaction.

Cavagnis[6] apparently was the first to employ living tubercle bacilli as immunizing agents. He added carbolated water to sputum which, with its living tubercle bacilli, was administered to animals, at first in small doses and later in gradually increased dosage, in the hope of producing immunity. In 1889, Grancher and Ledoux-Lehard used the same method of increasing doses to vaccinate rabbits with avian tubercle bacilli.

Dixon[7] thought it was possible by a thorough filtering-out of bacilli from tuberculous material that a filtrate would be obtained and attenuated so that by systematic inoculations a chemical or physical change might be produced in living animal tissues that would enable them to resist tubercle bacilli whose virulence had been diminished. Thus he conducted some experiments and thought he obtained resistance to tuberculosis in rabbits by introducing involuted forms of tubercle bacilli.

Daremberg[8] inoculated guinea pigs with dried spinal cords of tuberculous rabbits in an attempt to immunize them against virulent tubercle bacilli which he later introduced. He also used bone marrow from tuberculous animals (he had found tubercle bacilli in bone marrow and thought it might be a naturally attenuated vaccine). Animals injected intravenously with this material, and later with virulent tubercle bacilli, survived for from 5 to 15 days longer than control animals, but all died later from tuberculosis. Daremberg concluded that low, continuous absorption of the poison of the tubercle bacillus gives some immunity.

Grancher and Martin[9] inoculated rabbits with cultures of tubercle bacilli whose virulence had been attenuated by long growth on artificial mediums. These injections were made either subcutaneously or intravenously. Later these animals were injected with progressively younger cultures and thus more virulent bacilli. When they were finally infected with virulent tubercle bacilli, they lived longer than did controls.

Héricourt and Richet[10] injected into animals the soluble products of cultures of tubercle bacilli before introducing virulent organisms. In other animals they used living avian tubercle bacilli, hoping that enough resistance would develop so that the animals could defend themselves against virulent organisms later administered.

These various workers, beginning with Falk, who tried so desperately to immunize or increase resistance of animals to tubercle bacilli, obtained results which at first seemed hopeful but which ultimately failed. The general opinion developed that tuberculous infection differs with reference to resistance, as it does in many respects with some of the other infections. It was well known that an attack of smallpox, measles or typhoid fever usually results in considerable protection against subsequent attacks, whereas a bout with tuberculosis conferred no dependable immunity upon an animal. Thus it

appeared that there was little or no likelihood of ever being able to produce an efficacious immunizing agent.

Marfan's Law Based on Inadequate Observations

As the French workers were arriving at their well founded conclusion, however, Marfan[11] published a paper containing statements which became known as Marfan's law. They were to the effect that persons who presented healed scars from tuberculosis of the skin, as well as those who had recovered from tuberculous lymphadenitis, never developed pulmonary tuberculosis. No one doubts Marfan's integrity, but his conclusions were drawn from insufficient evidence. His subjects had not been observed long enough for the truth to be revealed. It was not until such persons had been observed, not for one or five years but for much longer periods, that the truth came to light, namely, that anyone who has had an attack of clinical or even primary tuberculosis in any part of the body and apparently has recovered is in considerable danger of having reactivations of old lesions or the appearance of new ones at some later time.

For example, Thompson[12,13] observed 324 cases of tuberculous cervical adenitis. During his period of observation, 54 patients developed pulmonary tuberculosis, of whom 13 died. He said: "Healing of the disease in the neck should not necessarily cause the patient's name to be removed from the dispensary register, but should be closely observed for the appearance of pulmonary tuberculosis throughout the remainder of their lives." Long periods of observation have established the fact that persons who have had tuberculous pleurisy, and have been apparently well for months or years, later fall ill from clinical tuberculosis elsewhere in their bodies in considerable numbers. Thompson[14] followed 190 cases of pleurisy with effusion for from one to eight years. Clinical tuberculosis developed in 12 per cent in the first year, in 8 per cent of the remainder within the second year, and in a total of 25 per cent within five years. In 15 per cent of these cases the first evidence of clinical disease was extrapulmonary.

Persons who have had pulmonary tuberculosis, minimal or advanced, and have apparently made excellent recoveries, are in danger of having old lesions reactivate or new ones appear years or decades later. Individuals who have no evidence of tuberculosis whatsoever by examination, except allergy of the tissues to tuberculoprotein as manifested by the tuberculin reaction, may have clinical lesions appear years and decades after the original primary lesions were apparently well controlled.

These facts recently (1951) were expressed by David T. Smith,[15] president of the National Tuberculosis Association, as follows:

> Unfortunately, tuberculosis, unlike the diseases mentioned above (he refers to typhoid fever, smallpox, etc.), induces little if any immunity. Indeed, as everyone knows, the patient who has recovered from clinical tuberculosis is even more likely to have a second attack than someone who has never had the disease.

These facts were not known to Marfan at the time his law was established, and therefore his statements misinformed and misdirected workers everywhere to seek a method of artificially producing immunity.

Tuberculin Also Failed to Produce Immunity

On August 4, 1890, before an international medical conference in Berlin, Robert Koch announced that he possessed a substance which would not only cure tuberculosis but also prevent it.

> Medical men from all over the civilized world flocked to Berlin to witness the effect of the remedy and to obtain some for their own use if possible. A thousand dollars was freely offered for a bottle which contained about a teaspoonful, and the substance could not be procured at that price from those who had been fortunate enough to procure same. Crowds paraded the streets of Berlin chanting rhymes in Koch's honor and shouting his name.

Koch said it was "a substance which, when inoculated into a guinea pig, renders this animal insusceptible to inoculation of the tuberculous virus. This same substance, in guinea pigs that are already afflicted with advanced and generalized tuberculosis, brings about a complete arrest of the development of the disease

although the animal organism does not suffer the least harmful effect under the influence of the remedy."

Thus, in his first presentation, Koch gave no description of his "curative and preventive" substance. However, in 1891, he stated that it was a glycerin extract of pure cultures of tubercle bacilli which, at first, was known as Koch's lymph. Before Koch revealed the nature of his substance, Bujwid[16] concentrated glycerinated liquid cultures of tubercle bacilli and obtained a substance that acted in the same manner as Koch lymph, which he named tuberculin. It was essentially the same substance and Koch later accepted the name tuberculin for his product, which has since been known as Koch's original tuberculin (OT).

Trudeau,[17] in the late 80's, was also seeking a method of preventing tuberculosis. In November 1890 he published an article stating that he had not been able to immunize animals with dead tubercle bacilli or with filtered and sterilized cultures. The substance he had used was essentially the same as that which Koch had employed. Concerning this, Krause[18] later said, "Trudeau published negative results and his paper was passed over without notice. Koch made startling positive assertions and his announcement created a furore."

From the time of Koch's announcement of the curative and preventive qualities of this substance to the present day, no one has ever made an animal or a person more resistant than normal to tubercle bacilli by the administration of tuberculin.

Concerning Koch's tuberculin experience, Krause[18] said:

> Koch's forte—his outstanding genius—lay in the invention and pursuit of bacteriological method. In this field no one has ever stood near him. Put him to the test of devising means to isolate and cultivate the obscure germs of a disease, and he could devise, adapt and put into practice procedures that seemed entirely beyond the ken and the imagination of the ordinary man. In this respect he was eminently Teutonic and exhibited the one outstanding talent of his nation in scientific endeavor, that is, a genius for the perfection of method. When it came to the formulation and development of the philosophic principles of science or to the interpretation of the results of experiments on animals, Koch's own publications must stamp him as being often sadly deficient. . . . He was entirely in error in 1890. Because of the tremendous weight of his authority, his announcement did a corresponding amount of harm. It is difficult to imagine why Koch, then the greatest name in tuberculosis, treated the responsibility of a great name so lightly. As time went on he little by little retreated from his dogmatic assertions on the merits of Old Tuberculin; yet at least twice more, in 1897 and in 1901, he made claims that were almost as extravagant and just as unfounded in support of two other types of tuberculin—the T.R. (Tuberculin R) and the B.E. (Bacillus Emulsion)—which he brought forward as his own inventions and which for a time he asked the world to accept as sovereign methods to combat tuberculosis. These more or less discreditable episodes in Koch's career have been the objects of no little speculation, and several ingenious theories have been brought forward to explain away his behavior which stepped beyond the bounds by which we define the scientific. To me the most plausible explanation has always been that whenever tuberculosis was under investigation and whenever Koch left his bacilli and his cultures and his staining methods and went over into the more subtle fields of tuberculosis as it may be produced in animals under controllable conditions, he got beyond his depth. . . . Koch's mind was so constituted that he could lay bare a cause to perfection, yet the effect, the disease, remained as baffling a problem as ever. It not infrequently led him into error.

Koch's Phenomenon Misleading

In 1891 Koch wrote:

> If one inoculates a guinea pig with a pure culture of tubercle bacilli the wound usually closes and for the first days seems to be healed. It is only on the tenth to fifteenth day that there appears at the point of inoculation a hard nodule which soon opens and forms an ulcer which persists until the death of the animal. Now such guinea pigs infected for from four to six weeks and again inoculated behave very differently. No nodule is now formed at the point of inoculation, but the next day or the day after, the site becomes hard and has a violet-red colour, then blackens over a spread of one-half to one centimetre. The following days the skin undergoes necrosis. The slough is thrown off leaving a superficial ulcer which heals rapidly without the neighboring lymph nodes becoming enlarged. Thus the injected bacilli behave quite differently beneath the skin of a guinea pig already infected than they do in a healthy guinea pig. This curious effect is not only with living bacilli but with dead bacilli.

This observation became known as Koch's phenomenon. The difference in reaction to infections in the skin was promptly interpreted by

many as indicating that the first infection had resulted in immunity. Although the second infection resulted in induration of the skin, which turned from violet-red to black within a few days and later necrosed, sloughed and left a superficial ulcer, the facts that it appeared to heal promptly and that involvement of regional lymph nodes was not in evidence deceived Koch and his followers. It is now known that factors which Koch did not understand—particularly the sensitivity of the tissues to tuberculoprotein which resulted from the first infection—were responsible for temporarily holding the tubercle bacilli of the second infection at the site of inoculation. He did not know that the bacilli of the primary inoculation resulted in no demonstrable lesion at the site of administration for 10 to 15 days because the tissues were not allergic during this period. When the tissues did become allergic, the few bacilli remaining at the site of inoculation produced a lesion through their protein which was then poisonous to the tissues. The other bacilli lodged in more vital points destroyed the animal.

The guinea pig was not a good animal for Koch's experiments for it is well known that a single injection of virulent tubercle bacilli into a previously uninfected animal will result in death from tuberculosis, hence the use of the guinea pig inoculation in diagnosis today. The superimposed infection on one that alone would result fatally could prove nothing with reference to immunity.

Although Koch's phenomenon has been heralded around the world as evidence that an animal develops immunity from its first infection with tubercle bacilli, no one has yet proved that anything more than allergy of tissues to tuberculoprotein was responsible for what he observed.

Koch's experiments were incomplete. If he had produced allergy in animals by introducing dead tubercle bacilli, he would have observed the same reaction when virulent bacilli were later introduced. Although the skin lesions appeared to heal and no regional lymph nodes were in evidence, if he had watched these animals sufficiently long every one would have died from tuberculosis.

Despite the inadequacies of Koch's experiment and the erroneous interpretation in the light of subsequent knowledge, to this day Koch's phenomenon is used as an argument to favor attempts to artificially produce immunity in animals and people.

Dead Tubercle Bacilli Tried as Vaccine

While studies were in progress to produce immunity by injecting living tubercle bacilli, there were physicians who believed the organisms should be killed before they were introduced into animals and people. Certain ways of killing bacilli were thought to have some influence on their supposed immunizing power.

Dembinski[19] used heat and reduced the bacilli to a powder. He injected this substance into rabbits in seven increasing doses after which, he thought, they manifested some resistance to virulent organisms.

Calmette[20] pointed out that it is not possible to confer lasting resistance upon guinea pigs by repeated injections of dead tubercle bacilli subcutaneously or intraperitoneally. Such injections cause the formation of abscesses or peritoneal lesions which result fatally. However, he and Breton[21] caused young guinea pigs to ingest 2 cg. of bacilli which had been heated to 100° C. On two occasions, 45 days after the second dose, the animals ingested virulent organisms. Calmette stated that the immunity so realized was only relative and not permanent. All the animals died after five or six months with pleural, hepatic and pulmonary lesions. Calmette and Guérin[20] found that tubercle bacilli, killed by heat of only 65° C., did not produce lasting resistance in cattle.

Loeffler[22] believed he produced partial immunity by using bacilli which were first dried cold and then heated to 71° C. from 9 to 15 days. He thought the capacity for resorption of the bacterial bodies within the animals was increased by this prolonged dry heating. Dogs vaccinated with this substance temporarily tolerated more bovine and human type tubercle bacilli than usual.

In 1906 Raw[23,24] began to make monthly subcultures of human, bovine and avian tubercle bacilli. At the eighty-fourth generation they

were markedly decreased in virulence. He used these organisms as a vaccine but first killed them by heat. The vaccine made from the bovine bacilli was administered to people and vice versa. Raw claimed to have obtained excellent results. In 1937 his cultures had passed through the three hundred and sixtieth generation and were still said to be avirulent and nonpathogenic. However, he still insisted that the organisms be killed before injecting the vaccines into animals and people.

Several workers produced so-called vaccines by destroying the vitality of tubercle bacilli with chemical reagents. For example, Moussu and Goupil[25] placed tubercle bacilli in 10 per cent Javelle water where they disintegrated in about three days. This material was then centrifuged, washed and neutralized before being introduced into animals. Several administrations were made. They concluded that when this material was used in small amounts in dogs and rabbits, some resistance developed. Calmette and Breton[29] used chlorinated bacilli in two doses ingested by guinea pigs. This afforded no protection against 1 cg. of virulent tubercle bacilli which the animals later ingested.

Vallée[26] introduced into the jugular veins of young cattle tubercle bacilli which had been macerated in 1:400 solution of iodine water. Rappin[27] treated tubercle bacilli with sodium fluoride and used them as a vaccine for cattle. Noguchi[28] treated one group of tubercle bacilli with sodium or ammonium oleate, another with oleate of neurine, and a third with oleic acid. All of these were used in an attempt to vaccinate animals. Any so-called resistance that developed was fleeting. Deycke and Much[29] suspended tubercle bacilli in contact with ovolecithin. These organisms were injected into 27 animals, of which 10 were said to be completely immunized and 8 partially so; 9 offered no resistance to virulent tubercle bacilli. Lindemann[30] macerated bacilli in lecithin in an incubator for from one to four weeks. These were administered to guinea pigs, but none of the animals showed evidence of increased resistance to virulent organisms.

Passini and Wittgenstein[31] liquefied sputum from tuberculous patients at 37 to 40° C. under a layer of toluol with increasing atmospheric pressure. This was filtered through porous porcelain, and the filtrate was administered subcutaneously to persons with tuberculosis. These workers claimed to have produced an excellent autotuberculin vaccination which controlled tubercle bacilli and the bacteria of mixed infections. A reaction occurred at the point of inoculation and, when large doses of the substance were given, fever appeared. Following this, they thought there was definite improvement in the individual's general health.

A controversy arose as to whether various lipoids extracted from tubercle bacilli possessed immunizing power. A number of workers, including Vallée[26] and Seligmann and Pincus,[32] claimed to have proved that they did not. Others, including Deycke and Much[29] and Kleinschmidt,[33] stated that they obtained antibodies from animals which had received waxes of tubercle bacilli or pure lecithin injected or ingested. Calmette and Guérin[34] found that in cattle such lipoids did not result in resistance.

However, when tubercle bacilli were freed of lipoids by solvents without much change of their protoplasm, antibodies were produced in the animals that received them. Cantanizene[35] treated tubercle bacilli in methyl alcohol and then with petroleum ether. These organisms were then placed in a solution of Gram's iodine for 15 minutes. When injected into guinea pigs, resistance to tubercle bacilli was demonstrated. Vallée[26] removed lipoids from tubercle bacilli in a slightly different way and claimed to have produced marked resistance in animals to intravenous inoculations of virulent tubercle bacilli. Martin and Vaudremer[36] removed the fats from tubercle bacilli in a still different manner and claimed that they had good vaccination properties.

Although some of the fat-free bacilli preparations had their supporters as immunizing agents, time proved that they were inadequate.

Since chemical reagents have more or less severe effects on protoplasm of tubercle bacilli, it was proposed that a better method of producing a vaccine would be to kill the organisms by light rays. DiDonna[37] killed tubercle bacilli by exposure to sunlight. Henry[38] used ultraviolet rays. Organisms killed by these methods were used as vaccines.

In 1913 Von Ruck[1] made sweeping claims for the efficacy of a vaccine he had produced from dead tubercle bacilli. He promptly had a good many followers who were also promising to prevent tuberculosis by his method. As early as 1902, the Congress of the United States had passed a law prohibiting the sale of "any virus therapeutic toxin, antitoxin, or analogous product" in the District of Columbia unless such product was prepared at an establishment licensed by a board consisting of the Surgeons General of the Army, Navy and Marine Hospital Services. When Von Ruck announced his vaccine, the United States Public Health Service undertook an investigation which resulted in an unfavorable report. Therefore he was refused license. He then appealed to the United States Senate in May 1913. The appeal passed over to the Senate of 1914 (Document No. 641 entitled "The Report of the United States Public Health Service on Investigation of the Methods and Practices Employed by Dr. Von Ruck in Treating Tuberculosis and Rendering Persons Immune from Tuberculosis"). The license was not granted. Nevertheless, a great deal of this so-called vaccine was employed and in at least one state the Board of Health had to set up a regulation forbidding its use in children. Concerning this so-called vaccine, Sir Almroth Wright, London, said: "We should not use children for experimental purposes so long as we have plenty of mice, guinea pigs and monkeys."

More Attempts with Living Tubercle Bacilli

Pearson and Gilliland[39] inoculated an animal intraperitoneally with tubercle bacilli obtained from human sputum that had remained in a collodion capsule in the abdominal cavity of a bull for seven months, after which Ravenel found the bacilli in pure culture. In 1901 the same animal was inoculated intravenously with a suspension of tubercle bacilli, probably of human origin, which had been recovered in pure culture by Theobald Smith in 1895. This experiment, along with those on other animals, caused the authors to state that their studies tended strongly to show that cattle may be refractory to enormous quantities of tubercle bacilli from human sputum and that, in one case, there apparently had been an increase in the resistance to virulent cultures of bovine tubercle bacilli. From 1902 to 1905 they reported that different strains had different immunizing values and that avian cultures did not confer much immunity upon cattle.

In 1905 Pearson[40] called attention to attempts to control the spread of tuberculosis among cattle by vaccination with living cultures of tubercle bacilli of low virulence for the animals studied. In discussing the previous work of himself and Gilliland, he said that the lesions were quiescent and encapsulated in all the treated animals but that they contained living tubercle bacilli. Whether an animal or a person in whom tubercle bacilli remained alive in the lesions may be regarded as cured seemed questionable to him. Since it is not possible on most American farms to establish a separate herd of infected cattle, the alternative, he said, is to destroy all the animals that react to the tuberculin test. He then thought it impossible to test all the infected herds of a state or nation; therefore, he was hopeful that vaccination would prove successful. Until more experiments and observations were completed, Pearson thought vaccination should be applied only under such conditions as would permit exact observations to be made, and each vaccination must be regarded as a scientific experiment.

Von Behring,[41] after having made notable contributions in respect to diphtheria and tetanus, turned to study of the tubercle bacillus. He had maintained a culture of human type in the laboratory for six and one-half years; the virulence of this culture had become extremely reduced for guinea pigs. This organism was dried and administered intravenously to young calves in two doses, the first consisting of 4 mg. and the second of 20 mg. given six weeks to three months after the first. These animals were isolated in a special stable during the immunization period and for six weeks thereafter to prevent infection with virulent tubercle bacilli. They appeared to develop a definite resistance to virulent tubercle bacilli which subsequently entered their bodies. Von Behring's statements concerning the efficacy of this vaccine were so sweeping that its use became obligatory in

Hessie, Oldenburg, Mecklenburg and the kingdom of Saxony.

In 1902 Von Behring was Nobel laureate for his fine accomplishments on serums. He was also made a Count by the German emperor. By 1904 he was widely known throughout the world and his statements and writings were generally accepted. It was then that he said:[42]

> I presume it is generally known that I have succeeded in discovering means by which we are able to immunize cattle and protect them against tuberculosis, just as human beings are guarded against smallpox by vaccination. My preventive against tuberculosis, as well as Jenner's preventive against smallpox, consists of live bacilli. Please do not entertain the erroneous opinion that my immunizing substance has the same effect as tuberculin; tuberculin is of value for the diagnosis of tuberculosis in cattle, while my immunizing substance is a *preventive for tuberculosis in cattle.*

Von Behring was so insistent that his method of combating tuberculosis was as good as that of Jenner's in smallpox that he named it anti-tuberculosis jennerization. When it became obvious that this term was not applicable, the name was changed to bovovaccination. He was so convincing that the Prussian government constructed the Royal Institute against Tuberculosis near Marburg in 1904 to be operated under his direction. In this institute his vaccine was made for distribution to all parts of the world. He said:

> The stability of our immunizing substance is such that we are enabled to send it, even to very far countries, without fear of deterioration. Dr. Lorenz, the celebrated veterinarian, in his paper on my immunizing substance, states: "After all that I have seen so far, I am sure that here we have a method which insures success. This method is of immense value and surpasses all others as to cheapness and easiness of application. It will supersede all previously proposed methods and render them absolutely superfluous."

Soon bovovaccine was on trial not only in Germany and Hungary but also in France, Sweden, Denmark and Italy.[43]

In 1904 a firm of druggists in New York City sent the following letter to owners of cattle in the United States:

> We would like to call your attention to some facts in reference to combating tuberculosis in cattle, feeling sure that they will interest you. Tuberculosis in cattle has proved to be more destructive to these animals than all diseases put together. Aside from this, tuberculosis in cattle is more or less dangerous to human beings, especially to children, due to the consumption of milk. All measures taken so far to suppress tuberculosis in cattle have proved to be of no success; the strictest veterinary police and the most thorough sanitary institutions, supported by the use of tuberculin, have failed to check tuberculosis.
>
> The latest method of Professor v. Behring, whose name is world renowned, seems to have solved the problem as to the suppression of tuberculosis in cattle. Professor v. Behring has been working on this subject practically for quite a number of years, and his wonderful results are based upon thorough experimental work. We therefore have to deal with facts and not with theories.
>
> The method itself is comparatively plain and consists of two inoculations, the second one following the first 12 weeks later. The inoculation is especially opportune in calves and young heifers not exceeding the age of 6 months. The two inoculations will immunize them against tuberculosis for their lives. In order to render older cattle immune, a thorough examination, followed by a tuberculin test, has to be made before inoculating.
>
> We furnish the vaccine and have it also injected by our veterinarians, in order to be sure that it will be done properly.

Concerning this, Pearson (Philadelphia) said:

> It is not necessary for us to rely for our information upon the unsubstantiated claims of a business firm endeavoring to make money by the sale of vaccine against tuberculosis. Briefly, I may say that the claims in relation to the work of von Behring are exaggerated and in part they are without foundation. There is absolutely not the slightest evidence to show that by means of von Behring's immunization method cattle may be immunized "for their lives" or, indeed, that they may be immunized against tuberculosis from natural sources for a length of time sufficient to make the vaccinations at all valuable.

On March 17, 1905, the firm of druggists replied to Pearson's "unfounded charges." They said they had expected some opposition to the introduction of Von Behring's bovovaccine, for they knew that all great discoveries bring forth opposition and protests from inferior minds. The company offered to supply the bovovaccine free of charge on a few occasions "in order to prove to the country at large that in this bovovaccine the world had received finally its answer to this great problem of bovine tuberculosis." In closing, the company registered a protest to Pearson's statement to the effect that its claims were of the patent medicine variety.

Although enthusiasm ran high in Europe for a while, scientific minds of students of tuberculosis put the method to the test; it was found wanting. They observed that the so-called protection afforded by bovovaccine was of short duration. Some said three months, others not more than one year.

In the report of the United States Bureau of Animal Industry (1912), Schroeder[44] emphatically condemned bovovaccine as unfit for use in the control and eradication of bovine tuberculosis. He pointed out that several vaccinated animals at the Experiment Station developed meningeal tuberculosis and that two heifers had tuberculosis in their virgin udders.

Von Behring himself apparently became dissatisfied with his own bovovaccine, for in 1906 he presented a new substance which he called tuberculase. This, he said, was so prepared as to destroy the vitality of tubercle bacilli and yet to preserve their immunizing power. The bacilli were killed with chloral hydrate and suspended in an alkaline solution of milk sugar. Tuberculase was a semifluid, somewhat waxy preparation, easily transported and sold at a comparatively low price. It was injected subcutaneously several times during a month. Von Behring claimed to have treated cows with tubercle bacilli in their milk so successfully that the bacilli disappeared in a few weeks. His reports raised the hope that this substance might be used in controlling tuberculosis in humans, especially that children might be vaccinated with it. However, tuberculase did not stand the test of time.

Eber[45] reviewed the entire subject in 1916. He stated that whatever resistance was developed in cattle by bovovaccine was not sufficient to enable the organism or the animal to resorb the virulent test bacilli or even those introduced as vaccine.

Animals which received bovovaccine eliminated human type tubercle bacilli in the feces and through the milk for a long time. Griffith[46] found them in the milk of 2 cows which had been vaccinated only a few days after their birth.

Von Behring's claims concerning bovovaccine were so extravagant that many other workers became interested and encouraged. As his method began to fail, they introduced modifications which they hoped would result in a satisfactory method of immunization. There were many such persons, only a few of whom can be mentioned here.

Robert Koch, et al.[47] had tried to immunize cattle with human and bovine bacilli of attenuated virulence since 1902. They claimed to be able to immunize the ass and the goat against large doses of highly virulent bovine bacilli. Koch and Schutz made a vaccine from attenuated bovine bacilli which was given the trade name—Tauruman. This was delivered to German veterinarians as an emulsion. Despite the claims made for this method, it was later found that one month after Tauruman was introduced, all the organs of the recipients contained bacilli which produced tuberculosis in guinea pigs. The organisms were also excreted in the milk. The resistance that the animals were alleged to have developed was lost within nine months.

Heymans[48, 48a] placed selected and modified human type tubercle bacilli in a permeable facade of reed pith. This was inserted into the subcutaneous connective tissue of cattle. A Belgian commission put this method to the test on a large scale between 1908 and 1911 and made an unfavorable report.

Levy, et al.[49] treated tubercle bacilli with relatively harmless chemical reagents to avoid modifying their chemical fractions. They attenuated cultures by adding a 25 per cent solution of urea for one day. When this was injected into animals in 1 mg. doses, there was no immediate effect but, after two or three months, there was evidence of caseation of lymph nodes near the site of injection. They then treated tubercle bacilli with a 25 per cent solution of urea for two days, after which the organisms were said to be completely harmless and were thought to constitute a good immunizing agent.

Klimmer[50] prepared a mixed vaccine which he called Antiphymatol. It contained human tubercle bacilli attenuated by heat so they no longer were pathogenic for guinea pigs and human tubercle bacilli which, by successive passages through salamanders, were no longer pathogenic for mammals. This preparation was introduced by way of the jugular vein or subcutaneously. The resistance of cattle, said to be

acquired after two months, began to diminish at the end of one year. This vaccine proved to be no more efficacious than bovovaccine.

F. Marino[51] found that tubercle bacilli, after residing in the digestive tract of leeches for 15 or 16 months, lost most of their virulence for guinea pigs. From these animals they were cultivated in glycerin broth; then they were put through the cycle—leeches, guinea pigs, broth—repeatedly for five years. This living organism he proposed as a vaccine.

Rabinowitsch[52] reduced virulence of tubercle bacilli by adding small quantities of formalin to culture medium. Two milligrams of this material introduced subcutaneously into guinea pigs appeared to make them resistant to virulent tubercle bacilli a few weeks later.

MacFadyean, et al.[53] used avian type tubercle bacilli to immunize cattle and believed they conferred considerable resistance. They preferred this to human type, which so often was transmitted from cattle to man.

Many other workers prepared vaccines—such as Arloing,[54] Theobald Smith,[55] Ferran[56]—and a larger number put them to the test. None of these preparations resulted in more than temporary so-called resistance or immunity.

Use of Acid-Fast Bacilli of Cold-Blooded Animals

Dieudonné[57] and Weber and Taute[58] found that acid-fast bacilli of cold-blooded animals were devoid of so-called vaccinating capacity in mammals. It had already been shown that human and bovine bacilli do not multiply in cold-blooded animals and therefore residence in such animals does not change their virulence. However, in 1903 Friedmann[59] isolated an acid-fast bacillus from a water turtle which he highly recommended as a vaccine against tuberculosis in cattle and also as a therapeutic agent for tuberculosis in humans. Friedmann's claims were so sweeping that when he later came to the United States his preparation was in tremendous demand. Large numbers of people rushed to him to receive the benefit of his method. His popularity became so great that an institute was set up for him in New York City from which the vaccine was to be distributed to substations in every state. Just as the American public was most wildly enthusiastic over Friedmann's promises of the prompt control of tuberculosis, the New York Department of Health wisely issued an order prohibiting its further distribution.

Orth[60] introduced Friedmann's vaccine into guinea pigs where it lived for months and even years and, at times, produced tuberculous lesions which did not cause illness or death. The animals acquired resistance, he said, to virulent bovine and human strains of tubercle bacilli, as they survived longer than controls. It was already known that acid-fast bacilli of cold-blooded animals do not result in such so-called resistance and it was concluded, therefore, that Friedmann's preparations were not composed solely of acid-fast bacilli from the turtle but rather that they also contained human type tubercle bacilli. Whether these were present by intention or by contamination no one knows. Clinicians in Germany and the United States such as Wolff-Eisner and H. L. Barnes carefully studied Friedmann's vaccine but could not substantiate his claims as to its efficacy.

Living Virulent Tubercle Bacilli Employed

Prior to 1909, practically all workers had attempted to reduce the virulence of human and bovine types of tubercle bacilli which they introduced alive in the hope of producing immunity to tuberculosis. The first attempt to immunize animals and children with virulent tubercle bacilli was made by Webb[61-64] and coworkers of Colorado Springs. They operated on the theory that by giving minute doses of tubercle bacilli, beginning with one and gradually increasing the number, the body would become immunized and later tolerate the usual doses of natural infection. In a guinea pig they began with one tubercle bacillus, progressively increasing the numbers until a total of 141,000 had been administered. At the end of nine months no tuberculous lesions were found in the animal's body.

Using monkeys and rabbits, Gilbert, Forster and Lieb[65] reported similar results. Calmette had this method studied by Bruyant.[66] As a final

study, he injected into guinea pigs 4 bacilli at most once or twice with a few weeks' interval. The animals apparently remained in good health, but after from 12 to 18 months necropsy revealed discreet tuberculous lesions usually localized in the liver or mediastinal lymph nodes. The lesions were similar to those often found in children who had died from other conditions. These findings caused Calmette[20] to emphasize the danger of using virulent bovine or human type tubercle bacilli even in dosage of a few organisms to develop resistance or immunity to reinfection. He said, "This consideration should be enough to cause the discarding of the idea of accomplishing anti-tuberculous vaccination by direct inoculation, no matter how sparingly, of bacilli which are alive and virulent and, therefore, capable of setting up tuberculous lesions." Calmette's emphatic condemnation quashed the method probably before many children were harmed.

Bacillus of Calmette and Guérin

In 1906 Calmette and Guérin[67,68] published the results of their experiments on the mechanism of tuberculous infection in which they showed that animals easily contract tuberculosis via the intestine without leaving visible lesions in the walls of the digestive tract. This had also been demonstrated experimentally by a number of other authors, including Ravenel.[69] Calmette and Guérin observed that if a calf is fed a certain number of human type tubercle bacilli in two vaccinating meals with 45 days intervening, and then is tested against natural contamination by being stabled with animals bearing open lesions, a greater resistance is conferred than if bovovaccine is administered intravenously according to Von Behring's method. Thus, in order to vaccinate by way of the digestive tract, it was necessary to find a substitute for virulent, tubercle-producing human or bovine bacilli.

Calmette and Guérin were convinced that a number of workers, including Von Behring, actually had produced immunity in animals by introducing living tubercle bacilli of attenuated virulence. Although none of these many methods had survived, they believed that, if the right tubercle bacillus could be found and could be so attenuated that there was no possibility of its regaining virulence or producing lesions, it would be possible to immunize both animals and humans against tuberculosis. They were working with a highly virulent bovine type of tubercle bacillus which Nocard in 1902 had isolated from the udder of a tuberculous cow. They observed that this organism grew luxuriantly on a medium with a basis of potato or agar saturated with pure bile glycerinated to 5 per cent. While growing on such medium, its virulence also became markedly decreased. In fact, after about 70 replantings, calves would tolerate the injection of 100 mg. over a period of 18 months, whereas 3 mg. of the same strain of bacillus maintained in a parallel manner on ordinary glycerin-potato medium produced fatal acute miliary tuberculosis in calves of the same age within 28 to 35 days.[20] Those calves which received two doses of this bacillus of low virulence one month apart, and which one month later were given 3 mg. of virulent bacilli, did not develop symptoms but, when the calves were sacrificed at the age of 18 months or less, virulent bacilli which killed guinea pigs were still present in their lymph nodes.

When Calmette administered this bacillus to 8 calves in 1912, he kept only 1 control. Thirty days after the second administration he gave the 9 calves intravenous injections of 3 mg. of a virulent strain of tubercle bacillus. The control animal died in a short time, and the others, killed at different intervals, showed no macroscopic tuberculous lesion. Calmette and Guérin conducted further studies on cattle, with encouraging results. Enthusiasm ran high for the use of this organism in the control of tuberculosis among the cattle of the world. Although the animals which received this special so-called immunizing organism were not observed sufficiently long, Calmette and Guérin were convinced that they had produced the proper immunizing agent. In 1921 they gave it their names, *Bacillus Calmette-Guérin,* and it has since been referred to as BCG. In 1924 Calmette declared it a *virus fixé.*

BCG First Administered to Infants

Calmette and Guérin strongly recommended

BCG by the oral route for infants and, in 1922, Weill-Halle and Turpin[70] apparently were the first to venture such a project. This was limited to newborn babies of tuberculous mothers. The infants were removed from contact at birth and placed in tuberculosis-free areas where they were given three doses of BCG by mouth during the first 10 days of life. They were retained in this tuberculosis-free environment over a considerable period of time and developed less clinical tuberculosis, such as meningitis, than infants previously seen who had remained in contact with tuberculous mothers. The difference in mortality was attributed to BCG rather than to the absence of exposure to tubercle bacilli. Equally good results already had been achieved by such workers as Bernard and Debre[70a] and Grancher of France and by Hess [70b] of the United States without BCG.

In 1926 Calmette[71] still stoutly maintained that BCG was harmless and that its virulence was absolutely and permanently fixed. He said that its efficacy in safeguarding infants against immediate environmental contagion had been "demonstrated beyond doubt."

Controlled Study of BCG Refused

When leading clinicians of France and of other countries demanded scientific proof through carefully controlled studies, Calmette refused. He believed enough proof was already available and that a well controlled study would only be a waste of time during which the benefits of BCG would be denied thousands of children. Thus Calmette lost the confidence of scientists and outstanding clinicians in most parts of the world.

In 1927 Calmette[72,73] was the first to produce statistics on mass vaccination. He quoted Moine's study of 882 children to whom BCG had been administered by mouth. These children were from homes where tuberculosis existed. Tuberculous disease had caused death in 7 (0.8 per cent). Calmette also quoted Biraud, who reported that, among 1,537 children who had received BCG by mouth, 1.84 per cent died from tuberculosis. They had no controls but for this purpose Calmette took the figures from a tuberculosis dispensary which showed a 26 per cent mortality for infants in tuberculous families, and concluded that BCG lowered the tuberculosis mortality among children in tuberculous families from 26 to 1 per cent. The editor of the *British Medical Journal*[74] called attention to the absurdity of a 26 per cent tuberculosis mortality among children. It was then found that Calmette had erred and that the 26 per cent which he used for the controls represented the total mortality from all causes among the children in the tuberculosis dispensary. Thereupon Greenwood[75] showed that in Biraud's group of more than 1500 children the majority were untraceable. In fact, only 679 were available for study at the end of eight months and at the end of 12 months only 367 were traceable. In 1928 Calmette[76] attempted to prove his case in another communication, but Greenwood showed that he had blundered even more in the second article. Therefore, it is exceedingly misleading to read Calmette's two articles without knowing the circumstances.

The question arose as to whether BCG, grown on mediums other than bile-glycerin-potato, would regain its virulence. In 1927 Petroff,[77] Saranac Lake, New York, grew this organism on gentian violet-egg medium. Two different types of colonies developed, one of which produced progressive tuberculosis in guinea pigs. Calmette believed this was due to contamination. Although a sizeable number of laboratory workers were unable to recover virulent tubercle bacilli from cultures of BCG, there were those, such as Much,[78] Reed and Rice,[79] Begbie,[80] and Seiffert,[81] who confirmed Petroff's findings.

Almost immediately following Calmette's rebuke in 1927-28, one of the greatest medical catastrophies of all time occurred in connection with a BCG project at Lübeck, Germany.[82] Among 250 infants who supposedly received BCG, many fell seriously ill and 77 died from tuberculosis. Although it was never proved conclusively that this disaster was due to BCG with virulence regained, the circumstantial evidence was such that the decision of the court was that the vaccine had been contaminated with virulent tubercle bacilli.

Another group of suspicious deaths among children vaccinated with BCG was reported by

Gárdi[83,84] at Ujpest, Hungary. Tuberculous cavities were found in the lungs of 2 infants and later in a third who had been given BCG by mouth at birth. Although 561 infants already had been given BCG, the project was immediately stopped. Twelve vaccinated babies died in a short time, but the examinations were so incomplete that it was impossible to determine with certainty how many had tuberculosis.

Ariztia, et al.[85] reported that, among 10 children who received BCG at birth in a Chilean hospital, 4 later became tuberculous and necropsy of 1 revealed tuberculosis of the lungs and hilum lymph nodes.

BCG Tried and Discarded by Veterinarians

In the United States, veterinarians and their co-workers put BCG to the most rigid and carefully controlled tests.

According to Schroeder[2] (United States Bureau of Animal Industry), experiments carried out during 1927 were even less encouraging than those of 1926, which showed that BCG did not provide anything approaching complete immunity. Schroeder warned that the BCG vaccine is a living, attenuated culture of an originally virulent bovine tubercle bacillus, and that our present knowledge of the fate of living tubercle bacilli in the bodies of animals requires that we should be very careful about adopting any alleged method of tuberculosis control which requires exposure to living tubercle bacilli of any kind, type or degree of virulence. He referred to the wide and premature publicity that BCG vaccination had received, and said that it seems to have inspired much unwarranted hope that a door finally has been opened through which tuberculosis can be driven easily and speedily out of existence, a hope which tends to encourage a disregard for tried and proved methods to check human tuberculosis and which raises the question whether our fight against this disease among the lower animals is economically sound or at all necessary for the protection of public health. He said that while BCG was being tested we should not be too sanguine in our expectations, as history has given us other examples of specific agents for the treatment and prevention of tuberculosis which proved to be forlorn hopes. Tuberculosis investigators know and the public should be informed that the tuberculosis vaccines which are now receiving attention present no radically new ideas and offer no previously unconsidered method for fighting tuberculosis. He said that the reports on attempts to immunize against tuberculosis since the tubercle bacillus was discovered in 1882 would fill several large volumes and present the names of quite a large number of famous tuberculosis investigators. He was of the opinion that the fact that arrested cases of tuberculosis often recrudesce has the character of fairly good evidence to prove that tuberculosis may flourish in the bodies of those in whom immunity against it seemingly should be greatest.

> The true value of vaccines lies in the aid they give in the control of diseases of which the sources of infection cannot be located, or because of their character or number, cannot be destroyed or made harmless, and the complete eradication of an infectious disease through the use of a vaccine is an achievement of which we lack an example. Hence, if we give due weight to the low percentage of tuberculosis among our domestic animals, and to reports which show that the percentage among our cattle is markedly declining, and to the complexities and uncertainties with which an eradication campaign dependent upon vaccination would be encumbered, it is exceedingly doubtful, even if the BCG vaccine proved fully equal to the claims its authors make for it, whether it would be wise or profitable to permit its use to supersede our present, rational eradication methods.
>
> A number of persons seem to entertain the mistaken idea that the treatment of all dairy cows with the BCG vaccine would at once eliminate the danger from tubercle bacilli in the raw milk of tuberculous dairy herds. They should take into account that the vaccine does not cure tuberculosis; that it does not kill tubercle bacilli in the bodies of infected animals; that it does not prevent tuberculous animals from disseminating tubercle bacilli; that it does not prevent the development of tuberculous disease unless it is used before virulent tubercle bacilli have invaded the body, but that it does interfere with the use of the tuberculin test to distinguish between safe and tuberculous animals.

Schroeder and Crawford,[86] reporting on their studies on BCG in animals, said: "The above results clearly indicate that vaccination of cattle with BCG has no value as a means of eradicating tuberculosis in livestock."

In 1931 the United States Bureau of Animal Industry reported that every vaccinated animal as well as every control animal in each of three experiments contracted tuberculosis. There was very slight, if any, difference in the character and extent of the tuberculous lesions in favor of the vaccinated animals over the controls. The extent of infection appeared to correspond to the length of exposure. Of this work, they said:

> These results corroborate the Bureau's previously published findings and demonstrate that the use of BCG vaccine does not prevent animals from contracting tuberculosis when exposed and that lesions once established do not tend to resolve.

Special Committee on Tuberculosis of the American Veterinary Medical Association[87] in 1931 said that BCG is of uncertain and questionable value as an immunizing agent because of its possible reversion to high virulence and tendency to induce a carrier state. The committee said further that strong evidence has been brought out, showing that the increased resistance which may follow BCG vaccination as manifested by delay or a slower rate of progress in the development and progress of the disease is more often than not of brief duration. The report stated further that the present knowledge and status of BCG vaccination does not justify, in the opinion of the committee, the hope that the efficient control of the disease can be effected by the adoption of this method.

In the report of the Committee on Tuberculosis[88] of the United States Livestock Sanitary Association in 1931 the following statement is made: "In these circumstances, and in view of the experimental evidence and of the extensive trials of BCG vaccination, your committee is of the opinion that this method of immunization against bovine tuberculosis must still be considered as in the experimental stage, and in respect to its innocuousness and efficiency open to question."

In 1934 Watson[89] summarized his experiments with BCG in immunizing cattle against tuberculosis, which had extended over a decade. During this time 100 cattle had been used in the experiment. Fifty-four animals vaccinated with BCG and 36 unvaccinated controls already had been studied post mortem at the end of trials of varying duration. The incidence of tuberculosis in the aggregate was exactly the same in the vaccinated and unvaccinated cattle. According to age, the average degree of tuberculosis was less in the young, immature animals but greater in the maturing animals in the vaccinated class than in the unvaccinated. Disease which was very similar to that seen in the unvaccinated was found in the lymph nodes and lungs of the vaccinated cattle. The lesions of the vaccinated cattle showed a marked tendency toward caseous, caseo-purulent and exudative processes, with appreciably less fibrosis than in the unvaccinated group, in which the caseo-calcareous type of lesion was in great preponderance. These results were confirmed by Larson and Evans[90] independent of the Bureau of Animal Industry. The veterinarians of North America then proceeded with their long-since-established, fundamental tuberculosis control measures and accomplished results that have never been attained anywhere with the use of so-called immunizing agents.

Summary

1. Promptly after announcement of the discovery of the tubercle bacillus, the thought of producing an artificial immunizing agent pervaded the minds of many physicians and scientists. Almost immediately, Koch and others instituted experiments designed to discover such an agent.

2. Attempts were made to weaken or reduce virulence of tubercle bacilli on the theory that they would then be tolerated by animals while immunity was being developed. It was hoped that sufficient immunity would thus be established to protect against subsequent invasions of virulent tubercle bacilli. At first the method appeared encouraging, as animals infected with tubercle bacilli of reduced virulence later appeared to be protected against injections of virulent organisms. Such animals seemed healthy when the controls were falling ill and dying. A little later, however, the vaccinated animals also fell ill and died from tuberculosis. Thus they had not been protected against ultimate illness and death. The opinion was then expressed that tuberculosis differs from such diseases as smallpox, typhoid fever and diphtheria

in that an infection does not result in dependable immunity.

3. Marfan established a law (1886) to the effect that persons who had recovered from tuberculosis or had evidence of healed tuberculous lesions of the skin and lymph nodes would not subsequently develop pulmonary tuberculosis. He had not observed his subjects sufficiently long. Prolonged observation has since revealed that such persons develop clinical tuberculosis of the lungs and other parts of the body with considerable frequency.

4. In 1890 Koch announced that he had produced a substance (now known as tuberculin) which not only prevented tuberculosis in animals but also cured those which had extensive disease. Since that startling announcement no one has ever made an animal or a person more resistant than normal to tubercle bacilli by administration of tuberculin.

5. Experiments reported in 1891 resulted in what became known as Koch's phenomenon. This only demonstrated that first infection with tubercle bacilli results in hypersensitivity to tuberculoprotein so that a reinfection brings forth a more intense and specific response of the tissues with resulting necrosis. When this necrotic tissue sloughed from the skin of animals the lesions appeared to heal. Thus Koch believed this apparent healing process was the result of resistance established by the first infection. The apparent healing of these superficial lesions was deceptive, since all such guinea pigs later died from tuberculosis.

6. Some workers who were opposed to the use of living tubercle bacilli as vaccine made preparations from dead organisms. Different methods were used to kill them, such as heat, chemical reagents and ultraviolet light. At first some of these preparations also seemed to offer considerable promise, since animals which received them later appeared to resist injections of virulent tubercle bacilli definitely better than did controls. However, all the vaccinated animals later fell ill and died from tuberculosis. Therefore, this method was equal to but no better than the use of living tubercle bacilli of reduced virulence. In the United States, Von Ruck and his followers made sweeping claims for such a vaccine. He made a strenuous effort to have it licensed by the United States Public Health Service, but failed.

7. Numerous further attempts were made by a large number of workers early in the twentieth century to produce an effective vaccine from living tubercle bacilli of reduced virulence. Among the many vaccines that were produced, the one by Von Behring was most extensively used. Over a period of six and one-half years he had markedly reduced virulence of a culture of human type tubercle bacilli which became known as bovovaccine. This was intended to immunize cattle and he planned to make a vaccine from bovine type bacilli for the immunization of humans. With reference to efficacy, he likened bovovaccine to Jenner's vaccine for smallpox. Through immunization he believed that tuberculosis would soon be a disease of only historic interest. The German government constructed an institute where this vaccine was made for distribution throughout the world. It became obligatory in a number of German provinces. Von Behring had drawn conclusions without sufficiently long periods of observation. His vaccine was later proved to be of no more value than the many others made from dead or living tubercle bacilli which had preceded it. A great deal of pressure was exerted to have Von Behring's vaccine widely used in the United States. Veterinarians gave it a thorough trial but found it wanting.

8. Friedmann made a live tubercle bacillus vaccine from organisms isolated from a water turtle. He claimed this to be of great value in preventing tuberculosis and also in curing those who already had clinical disease. He came to the United States, where this widely announced preparation was in such demand that an institute was set up for him in New York City from which his vaccine was to be dispensed throughout the country by state subinstitutes. Careful investigation revealed that Friedmann's claims were not justified, whereupon the New York Department of Health prohibited its further distribution.

9. Living virulent human type tubercle bacilli in extremely small doses were employed by Webb and co-workers about 1909 to immunize animals and children. They started by introducing a single tubercle bacillus and gradually in-

creased the number on subsequent injections. Calmette had these experiments repeated on animals and came to the conclusion that it was an exceedingly dangerous procedure and strongly condemned it.

10. Calmette and Guérin markedly reduced the virulence of a highly virulent bovine type of tubercle bacillus which had been isolated by Nocard in 1902. When introduced into animals they thought this vaccine produced a high degree of resistance or immunity to virulent tubercle bacilli later administered. However, their animals were not kept under observation sufficiently long. They were so convinced of its efficacy that in 1921 they gave it their names, *Bacillus Calmette-Guérin,* since known as BCG. In 1924 Calmette declared BCG a *virus fixé.*

11. BCG was first administered to infants by Weill-Halle and Turpin in 1922. These infants were then isolated from contagious cases of tuberculosis, but the results were compared with unvaccinated children who had remained in environments contaminated with tubercle bacilli. More clinical tuberculosis developed among the unvaccinated and it was concluded that BCG was responsible for protecting the others. Calmette refused numerous demands of clinicians and scientists to conduct a well controlled study because he believed the efficacy of BCG already had been proved. Over the next few years Calmette's reports were severely criticized. Petroff studied BCG cultures in the laboratory and found that certain colonies produced progressive tuberculosis in guinea pigs. This was followed by the Lübeck disaster.

12. Veterinarians of Canada and the United States put BCG to a most rigid test in cattle. They found that vaccinated animals developed as much tuberculosis as did controls when later subjected to the same exposure to animals with contagious disease. They then discarded BCG and abandoned the hope of its being of value in their tuberculosis eradication program.

The references cited in this article will be included in the author's reprints. The second part of Dr. Myers' discussion will be published in the next issue of *Postgraduate Medicine.*

MEETINGS AND POSTGRADUATE COURSES

University of Minnesota Medical School, Minneapolis: Continuation course in gastrointestinal roentgenology for radiologists, October 20-25, at the Center for Continuation Study, Leo G. Rigler, M.D., course director. Visiting faculty will include: Dr. Olle Olsson, Sweden; Dr. Richard R. Schatzki, Cambridge, Massachusetts; Dr. Frederic E. Templeton, Seattle; Dr. Paul C. Swenson, Philadelphia, and Dr. Leon Schiff, Cincinnati. The annual Leo G. Rigler Lecture will be presented October 22 by Dr. B. J. Kirklin of the Mayo Foundation.

Rocky Mountain Regional Institute of Alcoholism, Denver: The Colorado State Department of Public Health, Colorado Commission on Alcoholism, and the Office of Graduate and Postgraduate Education of the University of Colorado School of Medicine will sponsor this institute in Denver September 30-October 2. Detailed programs and information are available from: The Office of Graduate and Postgraduate Education, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20.

Postgraduate Courses in Britain: Dr. Julian Landman, London, England, is now visiting in the United States and Canada to inform doctors of the facilities offered to Canadian and American physicians for postgraduate study in medical and dental schools in Britain. Interested doctors may reach Dr. Landman at the Royal York Hotel, Toronto, during August.

National Association for Music Therapy, Topeka, Kansas: Third annual meeting, October 30-November 1, in the Hotel Kansan. Applications for membership may be made to Mrs. H. Dierks, 5050 Oak Street, Kansas City 2, Missouri. Non-member physicians and musicians may attend meetings by paying a registration fee of $5.00.

Surgical Intrathoracic Cardiovascular Lesions

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The field of cardiovascular surgery has now become a complex field of surgical endeavor. Many exceedingly fine results are constantly being obtained. A general survey of the field is presented and some more detailed discussion is given of the surgical treatment of coarctation of the aorta and mitral stenosis.

J. W. KIRKLIN

In 1897 Sir Stephen Paget wrote that "surgery of the heart has reached the limit set by nature to all surgery and it is unlikely that any new developments can extend these limits." No informed surgeon today would hazard such a prediction as to the ultimate future of cardiac surgery. There are at present a host of such lesions for which surgical treatment is being employed.

We can contrast the statement of Paget in 1897, as to the ultimate future of cardiac surgery, with the host of intrathoracic cardiovascular lesions that are at present amenable to surgical treatment (Table 1). The lesions that can be treated satisfactorily by operation are marked with an asterisk in this table. To show how rapidly this field of surgery is advancing, I would say that we should have put an asterisk in front of aneurysms of the thoracic aorta primarily due to the contributions that Dr. Schafer has made, which I believe he has already told you about.*

Although operations are available for many of the other lesions listed in Table 1, they are not always satisfactory. I believe that satisfactory operations for these pathologic conditions eventually will be developed.

This field of surgery has fired the imagination of all engaged in it. In many instances a severely handicapped patient can be restored to a healthy, useful existence by means of a properly executed surgical procedure. Although the heartaches in this type of work are occasionally bitter, the rewards can be great.

I hope to be able to interest you in this group of diseases by presenting cases which will illustrate some of the problems which exist today in cardiovascular surgery.

Coarctation of the Aorta

The first patient unfortunately could not be here today, but I will tell you briefly about him. He is a 23 year old man who was entirely well but who went, as many people do, for a routine

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*Schafer, Paul W.: Use of a temporary arterial collateral circulation to permit occlusion resection and frozen vessel graft replacement of vital vessel segments. Postgrad. Med. (in press).

TABLE I

SURGICAL LESIONS OF THE INTRATHORACIC CARDIOVASCULAR SYSTEM

I. Lesions of the heart
  A. Stab wounds*
  B. Valvular lesions
    1. Mitral stenosis*
    2. Mitral regurgitation
    3. Aortic stenosis
    4. Congenital "isolated" pulmonic stenosis*
    5. Tricuspid stenosis
    6. Congenital tricuspid atresia with atrial septal defect*
  C. Atrial septal defects
  D. Ventricular septal defects
  E. Tetralogy of Fallot*
  F. Myocardial ischemia
II. Lesions of the pericardium
  A. Chronic constrictive pericarditis*
III. Lesions of the great vessels
  A. Patent ductus arteriosus*
  B. Coarctation of the aorta*
  C. "Vascular rings"
    1. Double aortic arch*
    2. Anomalous right subclavian arteries*
    3. Right aortic arch with left ductus arteriosus*
  D. Aneurysms of thoracic aorta
  E. Anomalous pulmonary venous drainage
  F. Obstruction of superior vena cava

*Satisfactory surgical treatment available.

physical examination. He was found at this examination to have high blood pressure. More careful study by his physician disclosed that pulsations could not be felt in his femoral arteries. The blood pressure in his arms was rechecked and found to be 220 mm. of mercury systolic and 110 mm. diastolic, while that in his legs was only about 100 mm. systolic and 70 mm. diastolic. This combination of findings, which can be elicited by any doctor examining this patient with care, is virtually diagnostic of coarctation of the aorta.

It is extremely important to this patient, as we shall see, that the diagnosis of coarctation of the aorta was made by the physician examining him. Of course, there are other confirmatory evidences of his disease which can be elicited. There is a thrill over his back where the blood is flowing through markedly enlarged vessels comprising the collateral circulation. This collateral circulation develops as a result of the marked aortic obstruction caused by the coarctation. The dilated intercostal vessels which carry a very large amount of blood cause pressure erosion of ribs and are responsible for the notching so characteristically observed in the roentgenogram.

In considering treatment for a patient such as this one, we must first inquire as to the prognosis should nothing be done. After all, we would certainly agree that a surgical operation must carry less risk than that of the disease for which the operation is performed. Otherwise, operation is hardly justifiable. This is very important in cases of coarctation of the aorta, since many of the patients appear in excellent health when first seen.

Reifenstein, Levine and Gross* reviewed 104 cases of coarctation in which necropsy was performed. Operation for the coarctation had not been performed in any of these cases. The average age of the patients at the time of death was 35 years. In 74 per cent of the cases the patients died of rupture of the aorta (23 per cent), bacterial endocarditis or aortitis (22 per cent), congestive heart failure (18 per cent) or an intracranial lesion exclusive of embolism resulting from bacterial endocarditis (11 per cent). Thus the prognosis of patients with untreated coarctation of the aorta is indeed gloomy.

We must now inquire as to the prognosis of this patient should he be treated by operation. Data on prognosis are available from many sources, but I shall base my remarks on our material at the Mayo Clinic. It has been our experience that this lesion is resectable in approximately 90 per cent of cases, and that great improvement or a cure will result in about 94 per cent of the cases in which the patients survive the operation. The operation mortality rate has been approximately 7 per cent.

I should like to emphasize that the operative mortality is by no means exorbitant. As a matter of fact, we have been fortunate in that in the last 87 cases in which resection has been performed there has been only 1 death. Furthermore it is important to emphasize that an extremely high percentage of the patients subjected to operation are obtaining an excellent lowering of the blood pressure. It is our hope and indeed our firm belief that this lowering of the blood pressure with the resultant lowering of the strain on the heart and blood vessels will markedly

*REIFENSTEIN, G. H., LEVINE, S. A. and GROSS, R. E.: Coarctation of aorta; review of 104 autopsied cases of "adult type," 2 years of age or older. Am. Heart J. 33:146, 1947.

increase the life expectancy of the patients.

It is our belief that the optimal time for operation in cases of coarctation is when the patient is about 12 years of age or at least between the ages of 12 and 20 years. This is so because it is desirable, at least in our opinion, to operate on an aorta which is nearly of adult size. Despite the fact that we are now using interrupted sutures for the anastomosis in most cases in order to allow the anastomotic stoma to grow, we cannot be certain that its growth will keep pace with the growth of the aorta. Therefore, whenever possible, we would like to defer operation until the patient is about 12 years of age.

There are, however, certain definite indications for advising operation at an earlier age. Certainly impending left ventricular failure, which can be seen in coarctation of the aorta even in early infancy and later in childhood, is an indication for operation to be carried out as soon as the heart failure can be controlled adequately. The occurrence of bacterial aortitis in the region of the coarctation should indicate treatment with antibiotics for about six weeks. After that, operation should be carried out regardless of the age of the patient. Some older children have intracranial hemorrhage as a result of the hypertension in the upper part of the body. It is our feeling at present that if the child survives this hemorrhage, and if his general physical condition can be improved, operation should be performed. Because of impending cardiac failure, we have operated in one case in which the patient was 10 weeks old.

I would like to show you another patient illustrating this situation. This is a very healthy little girl who was seen here in St. Louis at the age of 4 months by Doctors Lynxwiler, Smith and Babich, who were wise enough to be able to make the diagnosis of coarctation of the aorta. Operation was performed when the child was 4 months of age. An end-to-end anastomosis was done after resection of the stricture, and convalescence was satisfactory. The child is now 14 months of age, and I think you can see that she is a healthy, hearty little girl. The size of her heart has returned to normal and she has not had any further evidence of congestive heart failure. I think that these men have obtained a really brilliant result in this case.

Mitral Stenosis

The other lesion about which I would like to talk with you today is mitral stenosis. There are certain things that one wishes to know concerning a patient with mitral stenosis when one is considering operative treatment of this disease. First, one should know whether the patient actually has mitral stenosis. There can be little doubt that the presence of the typical apical diastolic murmur of mitral stenosis is the single most important feature in the diagnosis of this disease. Despite the many advances which have been made in the study of cardiovascular lesions, it is important to emphasize that the practitioner of medicine with his stethoscope is still in the best position to make this diagnosis. In the absence of the ability to hear this characteristic murmur, a physician will have great difficulty in making the diagnosis of mitral stenosis.

After it has been determined that the patient actually has mitral stenosis, one must ask whether the patient is incapacitated enough by the disease to require consideration of operative treatment. One must ask if the patient is able to do her housework or must stay in bed several hours a day. Inquiry must be made whether the patient has had more and more trouble with dyspnea and finds that she is unable to walk as far as she used to. Particular attention must be given to whether the patient has paroxysmal nocturnal dyspnea, which, of course, is an evidence of the occurrence of pulmonary edema. One must ask whether the patient is able to sleep in a flat position or, instead, must be propped up with several pillows in order to sleep well. Inquiry must be made regarding hemoptysis, for this is most probably an indication of pulmonary hypertension.

These are extremely important considerations, for it is our opinion at the clinic, at least at present, that in cases of mitral stenosis only those patients with significant disability are candidates for operation.

I would like to point out that this estimation of the degree of incapacity imposed by the disease depends not on specialized scientific equipment, but on the careful questioning of the patient.

One must next look for any features in the

disease which would make the patient unacceptable for operation. The physician should inquire whether the patient has had any recent attacks of sore throat or episodes of prolonged fever. One, of course, must ask about joint pains or swelling of the joints. Any evidence of active rheumatic fever would make one hesitate to operate on the patient, at least at the present time; therefore, the presence of an elevated sedimentation rate, joint pains with fever and the like would make one decide against operation for the time being at least.

Furthermore, any evidence of subacute bacterial endocarditis would make one defer operation at least until this infection was completely under control.

It is pertinent to inquire into the physiologic changes which are produced by mitral stenosis in a given patient, for the surgical treatment of the disease is based frequently upon an understanding of this pathologic physiology. The mitral valve, of course, is situated between the left atrium and the left ventricle. In the presence of a stenotic lesion in the mitral valve, the pressure in the left atrium becomes elevated, and the pressure in the pulmonary vein, the pulmonary capillaries, the pulmonary artery, and finally in the right ventricle itself becomes elevated. As time goes on and as the stenosis becomes more extreme, despite this elevated pressure in the pulmonary circuit, the left ventricle is unable to receive an adequate amount of blood for ventricular systole; therefore, it cannot put out adequate amounts of blood and the cardiac output falls.

By cardiac catheterization, of course, one can pass a catheter into a systemic vein, into the vena cava, into the right atrium, and finally into the right ventricle where an accurate estimation of the degree of elevation of pressure within the right ventricle may be obtained. The catheter can then be advanced into the pulmonary artery and, again, a precise measurement of the degree of pulmonary hypertension can be obtained.

As I said previously, we do not feel that the mere existence of mitral stenosis is an indication for operation. Indications for operation in cases of mitral stenosis are debatable and no doubt not at all completely settled. We believe that operation is indicated if one of the following conditions is present: (1) significant disability; (2) progressively decreasing tolerance to exercise (with increasing dyspnea); (3) paroxysmal nocturnal dyspnea (pulmonary edema); (4) hemoptysis, and (5) recurrent or chronic failure of the right side of the heart.

At the risk of repeating, I would like to say that we insist on evidence of significant disability before considering the advisability of performing an operation. Certainly, progressively decreasing tolerance to exercise with increasing dyspnea is an indication that the patient with mitral stenosis is beginning to have difficulty, and we feel, therefore, that operation should be considered. A patient with paroxysmal nocturnal dyspnea is in reality, of course, having episodes of pulmonary edema, and we feel that this occurrence is an indication for consideration of operative treatment in cases of mitral stenosis. Hemoptysis, indicating elevated pressure in the pulmonary artery, is an indication for operation. Certainly, recurrent or chronic failure of the right side of the heart with ascites and enlargement of liver signifies that the patient with mitral stenosis is beginning to have serious difficulty and we therefore feel that operation is indicated.

Whenever any of these factors are present, it is our belief that the outlook for a given patient is poor. It is well known that many patients with mitral stenosis survive to the age of 50 or 60 years, and occasionally longer, but we feel that, when this train of events begins to develop, the prognosis becomes significantly less good, and that the advisability of an operation should be considered.

There are, of course, certain contraindications to operation. These probably are not accurately settled as yet. We believe the presence of active rheumatic fever or of subacute bacterial endocarditis is an absolute contraindication to operation at the present time. The rest of these contraindications we feel are relatively unfavorable for operation but not necessarily contraindications. Certainly a patient more than 50 years of age is not as good an operative risk for mitral operation as is one less than that age. However, we have operated on 2 patients in their fifties. Both have survived operation, and

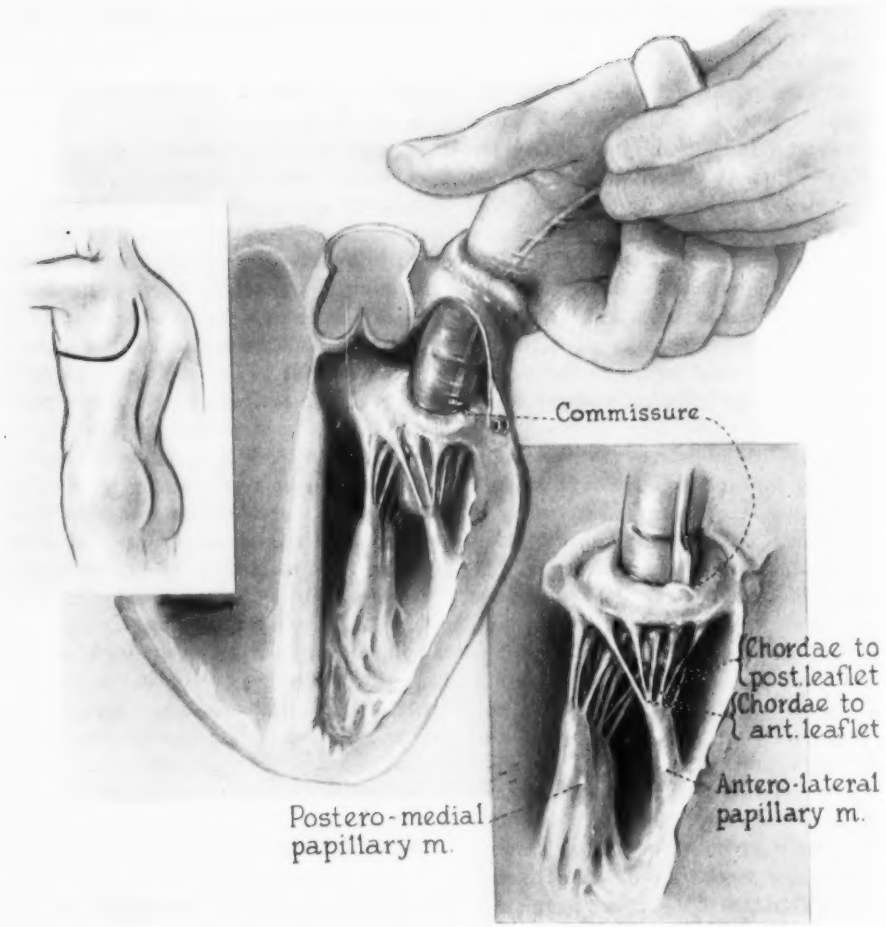

FIGURE 1. Mitral commissurotomy. Note that the knife is positioned accurately at the lateral commissure.

both seem to be getting good results, so this is not a final criterion against operation.

Marked cardiac enlargement has been said to increase the risk of operation significantly. I am sure it probably does increase it slightly, but again we have seen several patients with markedly enlarged hearts who seemed to survive operation very satisfactorily. If there is a severe associated valvular lesion such as a severe tricuspid stenosis or severe disease of the aortic valve, certainly one would not want to operate. However, patients with minimal disease of the aortic valve are not necessarily denied operation, since some of them have responded very well. The presence of a large atrial septal defect with a large left-to-right shunt is probably unfavorable for operation. A smaller atrial septal defect, however, is not necessarily a contraindication to operation in cases of mitral stenosis.

A history of arterial emboli has been said to be very unfavorable in a case of mitral stenosis in which one is considering operation. Certainly, it does increase the risk of operation, primarily because it imposes a hazard of such emboli occurring postoperatively. We have operated on 2 patients who had such a history. One

did have a postoperative embolus, fortunately a mild one, but survived. The other one got along all right. I think one certainly wants to be cautious in advising operation under this condition, but certainly it is not a contraindication to surgery.

Uncontrolled congestive heart failure is an unfavorable factor in considering a patient for operation, but once in a while such uncontrolled failure becomes chronic, and under such circumstances one is occasionally justified in advising operation.

It should be noted that mitral regurgitation has not been listed as a contraindication to operation. This is because, in our experience at least, we are unable by clinical evidence or by catheterization data to state with assurance in a given case of mitral stenosis whether or not mitral regurgitation also exists. Certainly, a systolic murmur in a patient with mitral stenosis does not indicate the presence of mitral regurgitation. Furthermore, we are becoming suspicious that it is uncommon for significant degrees of mitral regurgitation to accompany severe mitral stenosis. This opinion, of course, is in contrast to the belief which has been held through the years.

It is pertinent at this point to emphasize that a properly performed operation for mitral stenosis should not result in any mitral regurgitation, or in only a very limited degree of regurgitation.

Surgical Procedure

The operation itself may be very briefly summarized. We have been doing it through a posterolateral incision. The thorax is opened by resecting the fifth rib. The findings at thoracotomy are indeed dramatic. The pulmonary artery is usually hugely enlarged, being larger than the aorta and the superior pulmonary vein on occasion is as large as a man's wrist. A finger carrying a little knife is inserted into the left atrial appendage (Figure 1). We seek the commissures which are the sites of fusion between the anterior and posterior cusps. We incise the lateral commissure, extend the incision well out to the valve ring and, whenever possible, incise the medial commissure as well. The finger is then withdrawn, most of the auricular appendage is trimmed away and the resultant opening is closed with a few interrupted sutures.

It is important to inquire as to the mortality rate for this operation. Our experience is not as extensive as is that of some other groups working in this field. However, in a series of 20 cases we have had only 2 deaths. Our operative mortality rate is, therefore, 10 per cent. I believe that the mortality rate is going to continue to be between 5 and 10 per cent as long as we restrict the operation to patients who really need it and as long as we continue to operate on certain patients who have advanced heart disease. Personally, I believe in both of these policies. Approximately two-thirds of our patients have obtained a very good result as regards symptomatic improvement and reduction in pulmonary hypertension. Several of the remaining third have shown evidence of some improvement but not as much as we would like.

I should like to mention briefly one man, 36 years old, who had severe dyspnea, orthopnea and paroxysmal nocturnal dyspnea, all progressing over the past four years. Operation was done and he now sleeps flat, has no paroxysmal nocturnal dyspnea, and really feels very greatly improved. Before operation the pressure in the pulmonary artery was 122 mm. systolic and 60 mm. diastolic (the normal pressure is roughly 30 mm. systolic and 15 mm. diastolic). Five weeks after operation the pressure in the pulmonary artery was 44 mm. systolic and 21 mm. diastolic. This is certainly a gratifying reduction. His mean circulation time was 25 seconds before operation and 17 seconds after operation. His cardiac output before operation was 1.7 liters per minute per square meter, while it increased to 2.7 liters per minute per square meter after operation. Before operation his ventricle was able to eject only 27 cc. of blood with each systole; after operation it was able to eject 63 cc. of blood with each systole.

At the clinic, it is the opinion of those of us who have cooperated in the care and treatment of patients with mitral stenosis that operation for this lesion is sound and will continue to be an important part of the armamentarium for the treatment of this disease.

Management of Breech Presentation

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The principles which should guide us in the management of breech presentation are more important to keep in mind than detailed manual maneuvers. These principles are here reviewed and discussed with reference to this recurrent obstetric problem.

THE management of breech presentation is almost impossible to cover as a didactic topic. This is true primarily because one learns manual technics not by reading about them but by doing them. Also, if one were to describe in the most meticulous manner, step by step, the delivery in any individual breech presentation, it might well be found that not more than 20 per cent of the procedures outlined would apply to the next breech presentation encountered.

Rather than attempt such a discussion of manual technics in the abstract, therefore, it would be well to review some of the principles involved in breeches and their management—principles with which we are all familiar and which are neither new nor unique, but whose repetition might serve us in good stead when faced with an individual problem.

Etiology—The first of these principles, traditionally speaking, is the etiology of breech presentation. In general, it is an accommodation phenomenon; the fetus is accommodating itself to something in the uterus, in itself or in the pelvis. Statistically this is perhaps most frequently an accommodation to the location of the placental implantation, and Stevenson has shown that a cornual implantation of the placenta—in contrast to the implantation on either the anterior or the posterior wall—is characteristically associated with breech presentation. Or it could be accommodation to a pelvic contraction, to uterine fibroids or to a cord position. Fetal causes include accommodation to hydrocephalus or to a twin.

Prophylaxis—With these things in mind, how would one prevent a breech presentation? The purgation technic suggested by the South Americans some years ago has not proved successful in our hands, and external version—turning a breech presentation to a cephalic one by manual manipulation of the baby through the abdominal wall—remains probably the best preventive measure. Here lies the importance of considering the etiology, since external version is safer and more successfully accomplished if the factors which have produced the breech are known. Roentgenograms can reveal pelvic or fetal factors; soft-tissue roentgen technics will indicate placental localization. Careful auscultation of the heart tones during an attempt at rotation will indicate cord complications.

With respect to the technic of external version, the only suggestions to be made which might help are to do it during or after the thirty-sixth week (before that they may still correct themselves), and to move the fetal head toward the placenta first, in the case of cornual

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implantation. Care, gentleness and frequent auscultation of fetal heart tones are imperative.

The final point to be made under the heading of prophylaxis, of course, is: Never induce a breech. Purge them, turn them, leave them alone—but don't induce them. Some will turn themselves, some you will turn, some will come to section, but one of the contraindications for either medical or surgical induction of labor is the breech presentation.

When not to deliver—There are some patients left in whom prophylaxis has failed. Which of these will be scheduled for cesarean section? First of all, of course, the patient with pelvic measurements which are borderline or less. Even though one might vote for a test of labor with the same pelvis and the same fetus as a cephalic presentation, section should be seriously considered here. Second, the patient with uterine inertia and a breech; more will be said on this subject later. Third, and probably most important, the group of patients who have demonstrated a sharp limitation in their fertility, either in the actual past or in the potential future. This group would include the elderly primipara with a breech, the patient who is now pregnant after a prolonged period of previous sterility, the patient with fibroids, etc. These women have a demonstrated limitation on their total fertility. Given a breech presentation which cannot be corrected by external version, delivery should be made by cesarean section.

Even after setting aside the group which can be turned to a cephalic presentation and eliminating the group which will require section, there is still a group whose breech delivery is to be effected vaginally. With reference to this group and their individual management, we can offer only a series of axioms which can serve as more effective guideposts than can a discussion of individual technical points.

Guideposts to Breech Delivery

1. *A trial of labor in a breech presentation is of value in only one sense—to indicate the adequacy not of the pelvis but of the uterine contractions.* One is not testing to see if a pelvis is going to be adequate—we already have eliminated the borderline and contracted pelves. If a trial of labor is undertaken for these patients, it is with but one question in mind: How good are the uterine contractions? Actually, of course, the early hours of the first stage of labor in any patient represent such a test, and each patient should be seen during this time with this question in mind. In the breech, however, it is doubly important since, as already indicated, those patients with uterine inertia contribute to the group for whom cesarean section will be considered. Hence every first stage of labor is watched as an indication not of what the woman can endure but of what she can accomplish.

2. *The dilating wedge is less efficient—the cervix is occluded less completely.* Hence the first stage, on the average, will be longer and prolapse of the cord at the time the membranes rupture is more likely. The patient must be supported mentally; she must be hydrated, rested and nourished physically. And the fetal heart must be checked frequently and particularly as soon as the membranes rupture and the threat of cord prolapse increases.

3. *"Two and one-half hours in the second stage" is a rule designed to protect the fetal brain—it does not apply to the breech.* While one will not leave a patient too many hours in the second stage with a cephalic presentation, the buttocks neither impinge on bladder and bowel as does the fetal head nor do they suffer significantly after the cervix has been withdrawn up over them.

4. *Better an hour too long in the second stage than a minute too short.* This is simply to emphasize that there are far greater penalties resulting from too early initiation of the actual delivery than there are resulting from waiting longer to be sure that all cervical rim is out of the way. The degree of dilatation which lets the hips through is not necessarily sufficient to let the head through—it is better to wait, all other indications being equal, than it is to initiate delivery too soon.

5. *"Go and get", only 10 per cent. . . . The rest will come to you.* This figure is taken from our own count; actually the number of times one must reach high for a foot is limited. The unembarrassed baby and the mother in good condition will achieve a deliverance to the obstetrician in the great majority of instances.

6. *The episiotomy (mediolateral) should be one and one-half times the size the same baby would require as a cephalic presentation.* This is true both because the breech tends to follow the upper portion of the pelvic curve and hence drive downward toward the perineal body and because it is never known ahead of time when it will be necessary to insert a hand beside the fetus and assist from within. The median episiotomy, with its known incidence of third degree tears, is even more contraindicated here where extensions are so possible.

7. *For the maximum number of spontaneous deliveries of the buttocks, use light nitrous oxide anesthesia with or without pudendal block.* Either caudal or spinal anesthesia will reduce the capacity of the maternal voluntary expulsive efforts and thereby increase the number of times the breech cannot be successfully brought through the introitus spontaneously. Heavy general anesthesia, while excellent for intrauterine manipulations, detracts from both the voluntary and the involuntary expulsive force. Nitrous oxide in light concentrations (50 to 70 per cent), given only with the pains, will provide satisfactory pain relief until the baby has been delivered to the operator.

8. *The hips may be, but the back should never be, posterior.* While not infrequently the fetus will be brought down to sit in the hollow of the maternal sacrum, rotation so that the back will be lateral or anterior should begin promptly after this. Actually, of course, the hips can be brought down with the intertrochanteric diameter in the anteroposterior, and the less the fetal body is twisted the less the arms will tend to be swept up over the head.

9. *Nuchal arm trouble most often results from unindicated pulling.* To this one might add that since 80 per cent of the expulsive force comes from above, the most skilled attendant needs to be above rather than below the pubis. We are visualizing a delivery in which the baby is pushed out rather than pulled out. In addition to the retention of the maternal voluntary forces of expulsion, an able assistant who will keep pressure on the fetal head (not necessarily on the maternal fundus!), who will assist in keeping that head in flexion and thereby assist in keeping the arms down in front of the chest, is an invaluable ally.

10. *Finally it could be pointed out that, while there should be a sense of "unhurried haste" about the delivery of the aftercoming head, this applies only to the head; the delivery of the buttocks is always elective.* What particular technic is used for head delivery is probably immaterial as long as one avoids traction on the neck (the brachial plexus) and maintains the head flexed with the chin on the chest, and so long as most of the expulsive force is applied above the maternal symphysis and against the fetal occiput.

These, then, constitute a series of truths about the management of breech delivery rather than the description of any single case. By way of summarization it might be well to add some other more general aphorisms on this topic.

Have on hand: (1) bandage scissors—for cervical incisions in the patient dilated sufficiently to let the body through, but who traps the aftercoming head. Dührssen's incisions can be lifesaving in this situation; (2) a perineal retractor—the best way to provide air for the baby promptly is to depress the perineum, clear out the air passages and let it breathe. There is no reason the baby cannot start breathing prior to the complete delivery of the head if the perineum is held down out of the way.

The obstetrician needs: (1) increased patience—one will wait through a longer first stage, and throughout the episode interference carries a higher toll than in many other deliveries; (2) adequate assistance—consultation is invaluable and the "consultant" should be in the delivery room.

The patient needs: (1) general support and reassurance—to remove the fear and to support the body economy; (2) real instruction on the use of her voluntary expulsive forces—there is no need to ignore one of our best aids to safe delivery.

Herpes Zoster

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The present status of our knowledge concerning the etiology, epidemiology, pathology, clinical features and treatment of herpes zoster is discussed. Particular attention is given to the problem of ophthalmic zoster in the light of recent investigations of the phenomena of pain.

Our knowledge of herpes zoster presents on the one hand a specimen of workmanlike precision, but on the other it ebbs as a tide of confusion replete with speculation and conflicting opinion. The anatomic localization of zoster lesions and their general pathology are crisp and well defined. In fact, herpes zoster provided the original basis for Head's charts of radicular areas of sensory distribution. But the etiology of the disease, its pathophysiology and effective modalities of treatment are still matters of perplexity, conjecture and surmise.

Etiology

The etiologic agent of herpes zoster is generally conceded to be a specific virus.[1] Likewise conceded is that the zoster virus is distinct from the virus causing herpes febrilis, but closely related to the virus of varicella. Reports of the close relationship of herpes zoster and varicella have been too numerous to be ignored.[2-4]

The zoster syndrome also may follow mechanical or toxic injuries to nerve tissue and may occur in patients afflicted with tabes, cord tumors and other neurologic conditions, suggesting that there is a secondary type of the disease which is not due to an infectious agent but to trophic changes in the skin incident to nerve injury or disease. If such a hypothesis were true, the disease should be seen more often than it is under these conditions. A more widely accepted explanation is that the virus tends to localize and grow in irritated nerve tissue and hence zosters seen in the course of other neurologic conditions are etiologically and pathologically identical with zoster itself.[1]

Epidemiology and Incidence in Relation to Age and Sex

Herpes zoster is well stamped with the features of an infective disease. Malaise and fever often precede the characteristic neurologic and cutaneous signs. One attack confers almost complete immunity. The disease tends to show a seasonal variance, being more common in spring and fall; it is contagious; it may occur in small epidemics and its histopathology has the feature of a toxinfective reaction.

It is difficult to obtain accurate figures on the incidence and geographic distribution of zoster owing to its low mortality rate—only 14 deaths in 1948, according to the U. S. Public Health Service. However, zoster has been noted to

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occur in proportion of 1 to 2 per cent of all diseases affecting the skin.[5] In Veterans Administration hospitals there were 440 dispositions of zoster in 1949 with an average hospitalization of 20 days. In 1950 there were 513 dispositions with the same average length of stay. The incidence of herpes zoster in Veterans Administration hospitals almost parallels the incidence of Bell's palsy.

P. BAILEY

There are apparently two periods of life in which zoster is most likely to occur—under 14 and over 40 years of age. Men are more apt to be stricken than women, but the preponderance is not great.

Pathology

The central histopathologic lesions of zoster have been described by von Barensprung,[6] Head and Campbell,[7] L'hermitte and Nicholas,[8] Wohlwill,[9] Denny-Brown, Adams and Fitzgerald[10] and others.

The posterior spinal ganglia and their cranial analogues appear to bear the brunt of the attack. The most distinctive pathologic features comprise a ganglionitis marked by a necrosis of all or part of the ganglion with or without hemorrhage, and surrounded by lymphocytic infiltration.[10] But the process does not stop here. It extends to the meninges, the posterior root, the posterior horn, the anterior horn and the peripheral nerve. Invasion of the spinal cord follows the pattern of a poliomyelitis which resembles anterior poliomyelitis, but is distinguishable by its unilaterality, segmental localization and greater involvement of the posterior horn, posterior root and dorsal spinal ganglion.

Microscopically, there is necrosis and neuronophagia of nerve cells, microglial proliferation and lymphocytic infiltration of the perivascular spaces and meninges—a histopathologic picture which is characteristic of neurotropic virus infections.[10] Though not definitely established, it is believed by many that the virus migrates along the nerves to the skin.

Occasionally the pathologic process "breaks out" from its segmental confines to involve wide areas of the cord and cerebral tissues, giving rise to the clinical pictures of a meningomyelitis or a meningoencephalitis. Reports[11,12] of such cases with postmortem findings are few and far between, but the possibility of their occurrence must be borne in mind. Clinically they follow the usual pattern of viral infections of brain and cord.

Clinical Features of Spinal Zoster

The cardinal clinical manifestations of spinal zoster are radicular pain and paresthesias and cutaneous eruptions in the corresponding dermatomes. There is a selective vulnerability of certain spinal segments. Thus, in Head's series[13] of 394 cases the most vulnerable regions were the thoracic segments (72 per cent); next the lumbar segments (14.5 per cent); then the cervical segments (12 per cent), and finally the sacral segments (1.5 per cent). Of the thoracic segments the third to the fifth are the most commonly affected.

The disease is especially frequent in persons who are overworked or ill. It may occur on a background of other neurologic disorders. The illness usually begins with general symptoms—mild fever, anorexia and lassitude which last for a day or so. The next symptom, which often constitutes the first symptom, is pain, usually in the place where the rash afterward appears. The pain varies from aching and soreness to pain of great intensity, variously described as burning, gnawing, shooting, stabbing or neuralgic. The pain tends to be paroxysmal, is worse at night, is aggravated by movement or light touching of the skin, and may be relieved by heavy pressure on the skin. Paresthesias are almost always present and are recorded as irritation, itching, tenderness, pins-and-needles, heaviness, numbness, thumping, etc. They often persist longer than the pain and their severity appears to vary with the severity of the rash.

The initial pain and paresthesias tend to abate with appearance of the vesicles. When the latter fade, the sensory modalities of pain and touch may be impaired with or without enduring sore-

ness of the skin. After severe or pustular lesions, pale scars may remain which are insensitive to all forms of stimulus.

The cutaneous eruptions, which in the average case appear about four days after the onset of symptoms, begin as a patchy erythema with edema of the skin. The characteristic cluster of vesicles containing clear fluid then appears, usually in a patch of erythema. Usually discrete in parts, the vesicles, if close together, may coalesce and become confluent. The vesicles tend to be small or minute on the palm and sole and at the periphery of the limbs. The cutaneous eruptions are nearly always associated with a lymphadenitis arising from drainage of the affected field. This adenopathy disappears before the rash is gone.

The vesicular clusters tend to develop and spread where the posterior primary ramus and the lateral and anterior branches of the anterior primary ramus come to the surface. This vesicular band or "zoster belt," as it is sometimes called, following radicular lines, runs transversely around the trunk and more or less vertically over the arm or leg. The vesicular groups seldom occupy the entire dermatome, its limits being better delineated by the erythema. The lesions are almost always unilateral, though occasionally a few cross the midline.

In the average case the vesicles soon subside, dry up, scab over, and in a week or 10 days desquamate, leaving either shallow brown scars or faint marks difficult to trace. If secondary infection occurs, the lesions become hemorrhagic and pustular. These pustules either rupture, leaving in some cases a gangrenous appearance of encrustation, or begin to dry up. This crusting usually begins on the fifth to the eighth day of the rash and is complete within two weeks except in severely infected cases.

Motor disturbances in cases of spinal zoster are rare, only 44 cases having been reported in the literature up to 1943.[14] In all these cases the cutaneous eruption and the muscular involvement were on the homolateral side and in 90 per cent the rash and muscular weakness occupied the same segmental distribution. Conforming to the usual pattern of thoracic vulnerability, the trunk muscles are the ones most frequently involved.

The zoster rash almost always precedes the paralysis, the average interval separating them ranging from a few days to a few weeks. Complete recovery from motor involvement occurs in only about 15 per cent of the cases and requires six months to one year. The remainder have residual atrophy and weakness. The paralysis is of lower motor neuron type, although a few cases with signs of pyramidal tract disease have been reported.[15,16]

The cerebrospinal fluid is abnormal in about 40 per cent of the cases, pleocytosis (mostly lymphocytes) and increased protein count being the predominant features. These abnormalities are more prone to be extreme with zoster of the cranial nerves than with spinal zoster.

Most patients with spinal zoster recover without incident within 10 days to three weeks and present no special therapeutic problem. But severe infections, particularly those afflicting the aged, may result in the syndrome of postherpetic neuralgia which is a grave and unsolved condition of intense suffering. The same holds true for zoster of the cranial nerves, of which ophthalmic zoster is both the most common and the most serious. It is these forms of zoster that most frequently come to the attention of the neurologist.

Postherpetic Neuralgia

Postherpetic neuralgia has a high priority among painful neurologic syndromes for it may entail intense pain, panic and depression which sometimes lead to suicide. It attacks almost exclusively the aged with signs of arteriosclerosis. In general, a few weeks elapse from the termination of the acute stage to the full unfolding of the postherpetic syndrome. It is characterized by continuing pains, rising on occasion to paroxysms of intolerable sensation which may persist for months or years or to the demise of the patient. Burning, stinging, aching, crawling, pulling, boring and shooting are some of the terms used by patients to describe the pain.

Postherpetic neuralgia shows the characteristic element of selectivity of zoster infections by focusing on particular neural structures, namely, those that supply the trunk and the ophthalmic division of the trigeminal nerve (postherpetic

trigeminal neuralgia). Only rarely does it affect the limbs.

Zoster of Cranial Nerves

Among zoster infections of the cranial nerves, involvement of the trigeminal, facial, glossopharyngeal and vagus nerves are observed in general practice. These may appear singly or in combination. Zoster of the cranial nerves presents a more serious therapeutic problem than spinal zoster. It is more apt to be associated with postherpetic manifestations and other complications.

Ophthalmic zoster—Among the zoster infections of the cranial nerves, zoster of the ophthalmic branch of the trigeminal nerve stands out in bold relief for several reasons. It is the most common form of zoster next to thoracic involvement.[13] It is prone to be followed by a painful postherpetic syndrome and may give rise to dangerous ocular complications.

It is generally held that the gasserian ganglion provides the central focus of the trouble which spreads to the ophthalmic division and its branches. Clinically it is observed most frequently on the inner half of the upper eyelid, the adjacent side of the nose, over the eyebrow and in the region of the supratrochlear, infratrochlear, supraorbital and nasociliary nerves. These lesions are unilateral and often symmetric in design. The vesicles often are thickly set and almost confluent.

The real danger of ophthalmic zoster lies in the extension of the process to the globe of the eye. This occurs in about 50 per cent of the cases, causing disturbances in the transparent media, the iris, the sclera, the cornea, the optic nerve or the muscles. Edema around the eye may suffice to close it. Chemosis and keratitis may follow corneal invasion; ulcers may form and panophthalmitis be the result of secondary infection. Iritis, iridocyclitis, iridic adhesions and fixed irregular pupils may follow within the globe. Optic neuritis and atrophy, though seldom encountered, may occur. Argyll Robertson pupil and Horner's syndrome, even less frequent, have been reported.

Paretic phenomena of the ocular muscles occur in about 10 per cent of the cases of ophthalmic zoster. Most of the manifestations are referable to involvement of the oculomotor nerve, seldom to the trochlear or abducens—although cases of total ophthalmoplegia have been reported. Pareses of ocular muscles occur, presumably from extension of inflammation of the fifth nerve to the motor nerves as they traverse the cavernous sinus and the superior orbital fissure. These oculomotor complications have a higher incidence in elderly people, usually appear later than the rash, but may persist for a long time after the cutaneous eruption has disappeared.

It was once believed that ocular complications could not occur unless the nasociliary nerve was involved.[17] More recent reports of the occurrence of iritis and corneal scars in the absence of lesions referable to the nasociliary nerve have mitigated this notion somewhat. It appears now that the eye scarcely ever suffers much when the nose is not affected, and that the severity of the rash on the nose is in direct relation to the ocular pathology.[5] This does not mean, however, that the eye is exempt from invasion when the nose is not implicated.

Geniculate zoster—Among zoster of other cranial nerves, the so-called geniculate zoster or Hunt's syndrome[18,19] is worthy of mention. Here the vesicles are found on the auricle and less frequently on the anterior pillar of the fauces. There is pain in the ear and mastoid region, radiating to the anterior pillar of the fauces and to the vertex. The implication of the chorda tympani results in taste loss in the anterior two-thirds of the tongue on the homolateral side. There is almost always a facial paralysis, often associated with clonic facial spasm. The eighth nerve may become involved, leading to deafness or vestibular disturbances. For many years it was assumed that the disturbances associated with geniculate zoster had their pathologic counterparts in the geniculate ganglion. Recently this hypothesis has been challenged[10] and there is evidence that geniculate zoster may be of vagal or glossopharyngeal origin.

Diagnosis

A diagnosis of the average case of spinal zoster is too distinctive to be missed. There is

no other condition in which there is a vesicular eruption coupled with pain and hyperalgesia of a segmental distribution. Herpes febrilis ordinarily is bilateral, situated in the proximity of a mucous membrane and leaves neither residual pain nor scarring. Postherpetic neuralgia is distinguished from other types of radicular pain by the history of the eruption and the presence of residual scars.

Nonetheless, even the average case of spinal zoster requires complete examination of the patient, for it is to be remembered that it may occur on a background of other neurologic pathology, such as mechanical or chemical injury, toxic and infectious diseases and tumors of the cord. It is better to rule out these possible background disorders early than late. Zoster of the cranial nerves presents certain special diagnostic problems.

Patients with suspected ophthalmic zoster should be given a thorough examination of the functional state of the eye, including careful tests of visual acuity and extraocular movements. Geniculate zoster is probably more common than thought, due to misdiagnoses. In all cases of acute onset of facial paralysis, deafness, vertigo or laryngeal palsy, zoster vesicles should be carefully searched for, particularly in the auricle and the outer auditory canal.

Treatment

The treatment of herpes zoster should be considered from three aspects: (1) treatment directed against the infective agent; (2) care of the skin lesions and (3) management of pain.

The infective agent—As in most cases of virus diseases, specific treatment has shown little practical promise. Recently a ray of hope was introduced by a few optimistic reports on the use of AUREOMYCIN® and chloramphenicol.[20-25] But the hope stimulated by these early reports has been dissipated somewhat by the careful study of Carter.[26] In treating 11 patients with aureomycin (2 gm. daily for six days), 11 patients with aureomycin (4 gm. daily for four days), and 11 patients with chloramphenicol (2 gm. daily for six days), and comparing the results with those in 11 controls to whom a placebo had been given, he found no appreciable difference between the treated and untreated patients with regard to the appearance of fresh herpetic lesions, the amount and duration of herpetic pain, or the type, duration and frequency of paresthesias. But there was a marked difference between the controls and the treated cases with reference to the occurrence and control of secondary infection. Secondary infection was universally present in the controls but not in treated cases. Staphylococci were grown in the vesicle fluid of all the controls, but not in the treated cases. The results suggest either that treatment with aureomycin or chloramphenicol has no control over the virus in its effect on the nervous system, or that damage already has been done when skin lesions appear.

As a result of his study, Carter concludes that use of aureomycin and chloramphenicol in treatment of herpes zoster should be confined to two types of patients, namely: (1) cases of ophthalmic zoster, particularly in the elderly where it is likely that secondary infection plays some role in the severity of scarring or even in the production of postherpetic pain which so commonly follows, and (2) severe cases of spinal zoster, involving two or more segments, where the patient's life may be endangered by toxic effects or severe secondary cutaneous infection. Diabetic and nephritic patients would fall in this category.

Treatment of skin lesions—In the average case of spinal zoster the application of calamine lotion N.F. usually is sufficient. Protection from trauma and change in temperature can be provided by means of a thick layer of sterile cotton under a gauze pad supported by a binder. In ophthalmic zoster, it is essential to provide early protection of the cornea. As previously described, oral aureomycin should be given, and aureomycin solution should be used in the eye. Because of the potential dangers to vision, these patients require the advice of an ophthalmologist.

Treatment of pain—The treatment of pain and paresthesias comprises a major therapeutic problem in zoster infections. It is true that pain in the average case of spinal zoster presents no special problem, usually being adequately controlled by analgesias and mild sedation. But the problem posed by extremely acute cases and by

postherpetic neuralgia is still great and unsolved. The unsatisfactory condition of the treatment of zoster pain is reflected in the vast number of therapeutic devices proposed.

A case of postherpetic ophthalmic neuralgia will illustrate the number of procedures occasionally tried on one patient.[27] This 67 year old patient with postherpetic ophthalmic zoster received the following treatments: alcohol injections of the infraorbital nerve; a course in roentgen irradiations of the gasserian ganglion; partial division of the sensory root of the trigeminal nerve; division of all the sensory roots of the fifth nerve; cocainization of the sphenopalatine ganglion, and procaine block of the stellate ganglion. Since the pains persisted the same patient was given the benefit of an extirpation of the contralateral cortex of the face, which later was followed by extirpation of the ipsolateral sensory area as well. Pain persisted and due to agitation, suicidal thoughts and depressive tendencies, he was given a course of 16 electroshock treatments, resulting in a temporary indifference to pain which eventually returned. Finally, a bilateral prefrontal lobotomy was performed which did not eliminate the pain but, according to the patient's wife, rendered him more cheerful.

The confusion and inconsistencies appear to stem from (1) disagreement about underlying mechanisms of herpetic neuralgia and postherpetic neuralgia; (2) the fact that most zoster cases recover spontaneously, making it difficult to obtain adequate controls and to evaluate different therapeutic modalities, and (3) the confusion created by the vast number of reports in the literature, based on results obtained with only a few cases without controls.

There are two principal schools of thought in regard to the origin of herpetic pain. The first places the source of irritation centrally in the dorsal root ganglia, the nerve roots or higher up along the neural axis; the second believes it to be the irritated cells peripherally in the cutaneous sensory endings, the peripheral nerves or the sympathetic ganglia. Those who believe the source of the pain is more centrally located provide a rationale for injection or irradiation[28] of the dorsal root ganglia, dorsal rhizotomy, cordotomy and lobotomy. Those believing in a peripheral origin of the pain supply a rationale for vitamin B therapy, procainization or excision of the skin in cases where the irritative focus is considered to be situated in the sensory nerve endings, or for surgical PITUITRIN,[29] intravenous tetraethylammonium chloride,[30] paravertebral block,[31] or sympathetic ganglionectomy in cases where sympathetic mediation is believed to play the dominant role.

In addition to these procedures, other methods based more or less on empirical investigations are in vogue. Among these are autohemotherapy,[32] sodium iodide,[33] moccasin venom[34] and protamide.[35] Though the results are not uniformly successful, all the medical procedures mentioned have demonstrated effectiveness in certain cases of acute herpetic pain. How effective they are in preventing postherpetic neuralgia is not clear, but they seldom afford permanent relief to the postherpetic syndrome. The same holds true for the surgical procedures with the possible exception of excision of the skin and underlying subcutaneous structures—a procedure which requires further evaluation of a larger number of cases.[36, 37]

There is a current trend to distinguish between acute herpetic and postherpetic pain on neurophysiologic grounds. This tendency is to regard postherpetic pain as a reactive, "vicious cycle" type of pain caused by the activation of self-contained pain circuits in and above the thalamus. Bucy[27] advances the hypothesis that such self-contained circuits between the thalamus and cortical areas are activated and perpetuated by a lowered threshold at synapses, due to hypoxia attendant on cerebral arteriosclerosis.

These theories form a theoretical background for the use of frontal lobotomy and topectomy in cases of intractable postherpetic neuralgia. There has been some reported relief of postherpetic trigeminal neuralgia following lobotomy—manifested by a change in the patient's attitude toward the pain but not by an elimination of the pain itself.

The references cited in this article will be included in the author's reprints.

DIAGNOSTIC CLINIC

Acute and Chronic Osteomyelitis

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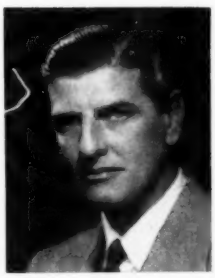
In acute hematogenous osteomyelitis, treatment is directed toward overcoming the generalized infection and controlling the local bone lesion. Use of sulfonamides and penicillin in a program of conservative treatment is discussed; 2 cases of acute osteomyelitis are described in which operative treatment was withheld. Emphasis is placed on the fact that in chronic osteomyelitis there is always a sequestrum or some situation subject to treatment; most such patients with chronic draining sinuses can be healed by a proper surgical approach.



R. M. O'BRIEN

THE story of the modern treatment of osteomyelitis began in 1936 with the work of Green and Shannon at the Boston Children's Hospital. These authors pointed out that the mortality rate of acute hematogenous osteomyelitis in infants could be tremendously reduced by withholding operative drainage of the bone lesion in the acute stage until the patient's condition had been strengthened by transfusions and other measures, and usually until the bone lesion had ruptured out of the confines of the bone and had become a soft-tissue abscess. They recommended only the simplest type of incision of the soft-tissue abscess, and pointed out that these measures reduced the mortality rate of this disease from as high as 40 per cent to about 10 per cent.

Several years passed and other changes occurred. The sulfonamides were introduced, and in 1941 Hoyt of the Akron Children's Hospital reported a series of 8 cases of acute hematogenous osteomyelitis in children in which operative drainage had been withheld altogether. Hoyt treated these patients by giving them large doses of sulfathiazole, the drug of choice at that time. He found that the incidence of recurrent draining sinuses and other complications was markedly reduced by this method.

Early in 1942 my associates at the St. Louis City Hospital and I decided to institute a program of conservative treatment for acute hematogenous osteomyelitis. Our plan was to administer adequate doses of sulfonamides (penicillin was not yet available) and to withhold operation. At the time this seemed like surgical heresy, since all of us previously had been taught that operative treatment in acute osteomyelitis was a surgical emergency not unlike that in acute appendicitis. However, the results of our previous efforts at operative treatment had been very unsatisfactory, with a mortality rate of about 20 per cent and many

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metastatic foci developing in other bones and joints, and we felt justified in trying conservative treatment. Also, we had frequently seen children who had more or less stayed home and treated themselves during the acute phase of the disease, and they seemed to have better results than did those patients who had been brought to the hospital promptly and treated by means of operation. So our series was begun independently of Hoyt's, but we were very encouraged later when his report was published.

In our series, sulfonamides lowered the mortality rate and seemed to control the systemic manifestations of acute hematogenous osteomyelitis very well, but they did not always control the local bone lesions satisfactorily.

For our series of 24 cases, the mortality rate was 4 per cent (1 death). The patient who died was a 5 year old boy who was admitted to the hospital only 18 hours after his first symptoms. At that time he was comatose and moribund. Blood and spinal fluid cultures showed a very heavy growth of hemolytic *Staphylococcus aureus*. Despite energetic and intensive therapy with intravenous sulfadiazine and intravenous penicillin, the child died in 15 hours.

The purpose of treatment in acute hematogenous osteomyelitis is twofold: (1) to overcome the generalized infection, usually a septicemia which threatens the patient's life, and (2) to control the local bone lesion.

The bacteriology of the disease is fairly constant. In children under 2 years of age the offending organism will be a *Streptococcus* in 90 per cent of cases. In children over 2 years of age the offending organism will be a *Staphylococcus* (usually a hemolytic *Staph. aureus*) in 90 per cent of cases.

The local bone lesion is essentially an inflammation within a rigid compartment. If antibacterial therapy is begun while the circulation in this area is still intact and before pressure and thrombosis slow circulation, the effect of these drugs should be very good, and that was our experience. In the later stages, when the process is well advanced and local circulation in the bone is blocked by pressure, thrombosis and swelling, the antibacterial agents may not be able to reach the invading bacteria.

The general signs and symptoms of the disease respond quite promptly to administration of penicillin. We found that the combination of the sulfonamides and penicillin had no special merit. The sulfonamides usually had to be discontinued because of toxic effects. The combination of streptomycin and penicillin might offer some advantages; however, most of the patients I have seen have responded well to penicillin alone. The fever subsides after 24 to 48 hours, and a prompt local response usually occurs also—within two or three days. Hot, wet packs are usually employed as an adjunct, particularly if the affected area is swollen and indurated. We use a very heavy type of hot, wet pack (woolen blankets) in such a way that they immobilize the part as well as provide heat. These packs are renewed every two hours.

Roentgenologic manifestations are worth reviewing. X-ray changes do not appear in osteomyelitis until about 10 days to three weeks after the onset of symptoms; that is, the earliest x-ray change occurs about 10 days after the first symptoms, but in some cases it does not appear for three weeks. The earliest change is an area of diminished density in the bone, usually circular in character, located in the metaphysis, the portion of the shaft adjacent to the epiphyseal line. The common sites are the lower and upper ends of the femur, the upper and lower ends of the tibia and the lower end of the radius; changes sometimes are seen around the elbow and around the shoulder.

Metastasis formerly occurred in about 25 per cent of cases. In penicillin-treated cases in which operative treatment is delayed, spread of the disease to another bone or another joint has been reduced to practically zero.

After several days of local swelling of the affected extremity, there will usually be response to the hot, wet packs and to the systemic administration of penicillin. Occasionally, however, when treatment has been delayed, the process will make an exit in some way from the bone and a soft-tissue abscess will develop.

The question of management of these abscesses is debatable, but we feel that in general they should not be opened surgically; rather, they should be aspirated with a fairly large-bore needle through adjacent normal skin. The reason for aspiration is to prevent spontaneous rup-

ture. The objective is to try to keep the infection a closed infection so that there is only one organism involved. If incision and drainage are done, the wound promptly becomes secondarily infected and a multiplicity of organisms enters the picture and new organisms are constantly being introduced. The host has no chance to develop resistance toward these new invading bacteria. Aspiration usually will control the soft-tissue abscess; sometimes repeated aspirations are necessary.

Chronic Osteomyelitis

I am sure you all remember from your student and intern days that outpatient departments were filled with people coming in for dressings for chronic draining sinuses. This situation has been almost eliminated. We have found that if there is persistent drainage of a sinus there is a reason for it, and that reason usually is a piece of dead bone somewhere in the depths of the wound. Often it cannot be seen by x-ray. This circumstance is illustrated by 2 patients whom I saw recently. One, a 27 year old woman, had had osteomyelitis of the upper end of the femur at the age of 7 years. She had about five persistent draining sinuses around her hip. We injected radiopaque substances but were unable to localize any sequestrum although the sinuses did lead down to the hip joint. We felt sure, however, that there was a loose piece of dead bone in her wound; if not, the process would have healed. Consequently, we opened her hip widely from the front and explored the anterior surface of the hip, but found nothing. When we turned her on her side and explored the hip posteriorly, we found a fairly good-sized piece of dead bone behind the neck of the femur. This bone was removed and within a period of two months all her sinuses healed and have remained healed.

The second case was that of a 57 year old man who had had chronic draining sinuses for 30 years. No sequestrum could be found on x-ray examination, but at operation a small piece of bone was found deep in the tissues about the hip near the acetabulum. This piece of bone apparently had acted as a chronic irritant to keep the infection in his wound alive.

Illustrative Cases

Case 1—A 10 year old boy, a doctor's son, had a swollen, painful right forearm with obvious signs of cellulitis of the forearm of about four days' duration when I first saw him. Because the swelling was circumferential and completely around the forearm, I felt it was an early osteomyelitis. A cellulitis or an abscess in an extremity generally will be on one side of the extremity and not completely surrounding it. Osteomyelitis is more likely to be circumferential. The boy was brought to the hospital. X-rays were made, but provided no pertinent information. He was given large doses of penicillin—300,000 units three times every 24 hours for the first two days, then two times every 24 hours for two more days, and finally once every 24 hours. He was also treated with hot, wet packs to the affected extremity.

After 10 days in the hospital, the boy was clinically well; the pain and the swelling had subsided. However, an x-ray taken at that time showed the typical findings of a very early acute hematogenous osteomyelitis—an area of diminished density in the metaphysis of the bone, in the shaft next to the epiphyseal line.

After one month the area of diminished density noted in the 10 day film no longer was present and the bone was completely healed. How different is this story from that of past years when, at the first stage, we would have done incision and drainage. Incidentally, in the present case, at the first stage this boy's forearm was swollen and generally tender, and you could not have been too sure of the location of the process—not even whether it involved the proximal or the distal end of the bone.

Case 2—A 12 year old boy had acute osteomyelitis at the upper end of the femur. This boy was seen before penicillin was available, and was given sulfathiazole or sulfadiazine. Although these drugs are not as effective in controlling the bone lesion as is penicillin, still they control it better than no treatment at all and also better than surgical evacuation of the abscess. At the end of five months the sequestrum had absorbed. There was some residual sclerosis of the bone, but the boy had a perfect functional result.

An interesting point concerning antibiotics in treatment of osteomyelitis is that sequestrums, if they are small and in contact with living tissue, can absorb spontaneously. If they are large, surrounded by pus and have lost contact with living tissue, they must be removed surgically.

The good results obtained in our series are due, I believe, to the fact that all the patients were seen early in the course of their disease. Treatment was begun, on the average, on the fourth day after onset of symptoms.

Early diagnosis is made by being suspicious of every abscess, inflammation, cellulitis—whatever you want to call it—every inflammatory process that occurs in the extremity of a child. Every such change should be considered as potentially osteomyelitis and should be treated by prompt administration of penicillin in adequate doses. Inadequate doses of penicillin might do the child a great disservice. If you do not give him enough to overcome the infecting organism, it may become penicillin-resistant. Prompt administration of penicillin in adequate doses usually will abort acute hematogenous osteomyelitis. As a matter of fact, the orthopedic surgeon rarely sees a case of osteomyelitis today, because the pediatrician or the family doctor already has detected it and treated the child, and in most instances the process is aborted.

There is one important point to remember. I urge that you do not operate promptly on patients with acute osteomyelitis. By that I do not mean that you should never operate on such patients; in general, operation is delayed and usually the only patients for whom operation is done now are those in whom the original treatment was inadequate and in whom there is fairly extensive destruction of bone and large sequestration. When we do operate, if at all possible we close the wound primarily following the operation, rather than packing it open.

In chronic osteomyelitis we believe there is always a sequestrum or some situation that is subject to treatment and that most patients with chronic draining sinuses—no matter what their duration—can be healed by proper surgical approach. Usually this means a tedious, painstaking operation through a difficult operative field in which there is a great amount of scar tissue and in which bleeding is difficult to control.

Finally, I would like to say a few words about acute inflammation in joints. The same rules do not apply as in bones. The old operative treatment of infected joints produced fairly good results, and if an infected joint does not respond promptly to the administration of antibiotics, then incision and drainage of the joint should be done. Irrigation of the joint should be carried out at the time of operation, and then the synovial membrane and capsule should be loosely sutured.

DIAGNOSTIC CLINIC

Duodenal and Gastric Ulcer

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I KNOW of no condition that has been the subject of more literature or more clinical and laboratory investigation than peptic ulcer. For a number of years I have reviewed the surgical literature on peptic ulcer for the *Journal of the American Gastroenterological Society*. It has been a tremendous job; we have abstracted an average of 500 to 600 articles each year and have by no means exhausted the material. Certainly, since Dr. Lester R. Dragstedt first reported on vagotomy for peptic ulcer, there has been an enormous amount of investigation of the physiology, operative procedures and clinical results relating to peptic ulcer.

I do not want to imply that surgical treatment of peptic ulcer is synonymous with partial resection of the stomach, and certainly I do not want to imply that vagotomy is synonymous with surgical treatment.

In no other field of medicine is there more need for integrated medical and surgical effort than in managing these patients with peptic ulcer. We had thought that the problem was fairly well settled; there were those who advocated gastroenterostomy and there were medical men who favored a medical regimen. However, when vagotomy was first described, we found that the whole subject was again brought into focus. Many patients with ulcers are now being treated by vagotomy and gastroenterostomy, and unfortunately many of them could be managed very satisfactorily with medical measures and proper diet.

S. F. MARSHALL

Over a 20 year period at the Lahey Clinic we have seen about 16,000 patients with peptic ulcer. This group included about 1000 cases of gastric ulcer and about 350 to 375 cases of jejunal ulcer. About 10 per cent were subjected to operation. This leaves a large group of patients, 90 per cent, who can be handled satisfactorily with good medical measures, and remember that the dividends of good treatment in these cases are enormous. The proper diet for a patient with an ulcer is not nearly so rigorous as the diet for a patient with diabetes, and the rewards again are tremendous.

About 57 per cent of our patients with jejunal ulcers and about 37 per cent of those with gastric ulcers have undergone operation, but there has been a great increase in the number of gastric ulcer patients who have had resections. Over a period of 20 years, we operated on only 121 patients with gastric ulcers in the first 15 years, whereas we have subjected 221 patients

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with gastric ulcers to operation during the last five years.

The problem of the complications of peptic ulcer (and these are the patients who should be treated surgically) is still unsolved to a large degree, and vagotomy has not added a great deal to the surgical treatment. I have a few figures of the Committee on Surgical Procedures in the Treatment of Peptic Ulcer of the American Gastroenterological Society which were given to me by Dr. S. M. Jordan, the chairman of that committee. The results are not too encouraging. Of course, it is a preliminary report and perhaps it will take many years before the place of vagotomy in the treatment of ulcer can be established. Undoubtedly there is a place for vagotomy. On the other hand, we are putting most of our reliance on the operative procedure of partial gastrectomy.

We have a patient here today. Mr. T. has an ulcer history of about 15 years. He is 48 years of age. (To the patient): Is that correct?

PATIENT: That is right.

DR. MARSHALL: His first symptom was severe abdominal pain. He had no hemorrhage, and no evidence of obstruction. In 1938, because of his pain, he had an appendectomy with no relief of his ulcer symptoms. In 1941 he had a gastroenterostomy and was able to get along fairly well without pain, distress, hemorrhage or obstruction. For a period of how long?

PATIENT: About five or six years. It came back on me in 1947.

DR. MARSHALL: In the meantime you had had no hemorrhage?

PATIENT: No.

DR. MARSHALL: Where was your pain?

PATIENT: It was at the lower ribs, down the side.

DR. MARSHALL: Would you say that you also had pain to the left?

PATIENT: Not a great deal.

DR. MARSHALL: But you had some pain there?

PATIENT: Yes.

DR. MARSHALL: How severe was your pain when it returned in 1947?

PATIENT: Well, there were slight attacks.

DR. MARSHALL: During the past year his pain became so severe that he was unable to work. He would return to work for a few weeks and then have to give it up because of the pain, and he also remarked that many of his friends thought that he was neurotic because he looked so well; in other words, he had had no evidence of hemorrhage, he was not anemic, he had no obstruction, so he had not lost a great deal of weight, but he had persistent and constant pain. Was the pain severe?

PATIENT: It was.

DR. MARSHALL: On September 28, 1951, he had a partial gastric resection. A jejunal ulcer was found which had perforated onto the mesentery, and there also was an activated duodenal ulcer, which often happens if the stomal orifice functions poorly. The ulcer appeared to be quite adherent to the gastrohepatic omentum and to the gallbladder. It was thought that it would be difficult to remove and that its removal might be dangerous, and a tube—a catheter technic—was used in the closure of the duodenum. Drainage was profuse for about 10 days, after which the tube was removed. Now how are you feeling?

PATIENT: I feel fine.

DR. MARSHALL: This is a good illustrative case of a jejunal ulcer developing after gastroenterostomy. I have seen instances in which these ulcers have developed as long as 21 years after a procedure of that type.

We have operated on 175 patients with jejunal ulcers and there also is a fairly large group which has been treated by medical regimens; in other words, not all these patients require surgical treatment for relief of their symptoms.

Figure 1 is a roentgenogram of a jejunal ulcer; the outline of the stomach and the ulcer niche can be seen.

Figure 2 shows a jejunal ulcer which developed following an insufficient resection of the stomach. Remember that jejunal ulcers can occur after any operation in which the jejunum is anastomosed to the stomach, but they occur most commonly after gastroenterostomy. Jejunal ulcers developed following gastroenterostomy in about 90 per cent of our group of 175 cases.

We also have a group of cases in which jejunal ulcers developed after resection, and in most of these the ulcer developed after an insufficiently radical resection. At least 70 per cent

of the stomach has to be removed in order to prevent this serious complication of peptic ulcer. Remember that this is a serious complication because it is evidence of failure of surgical treatment of ulcer (Figure 3).

There are some curious facts about jejunal ulcer. The pain ordinarily is to the left of the midline. Very commonly it may be difficult to demonstrate an ulcer niche.

In many of these patients, the stomal orifice between the stomach and the jejunum is tremendously narrowed and may even be occluded, or there may be a marked stenosis. As the result, the duodenal ulcer may be reactivated, as occurred in the patient I presented. This man had not only an active jejunal ulcer with perforation, but also a reactivated duodenal ulcer with perforation onto the gastrohepatic ligament, and this of course was deemed risky to attempt to remove. I think the surgeon handled the problem very well.

I would like to point out that hemorrhage is a frequent occurrence in cases of jejunal ulcer, but fortunately the prognosis for these patients is good and conservative treatment over a long period of time is justified. In our group of 175 operated cases, the incidence of hemorrhage was similar to that reported by Gordon-Taylor* (50 per cent). In a group of 70 cases that I studied, massive hemorrhage occurred in 34 patients.

Figure 4 illustrates still another complication, that is, the development of a gastrojejunocolic fistula. Penetration is one of the characteristics of an active ulcer and this may occur through the wall of the stomach into the pancreas, as is seen so commonly in duodenal ulcer. Surgical treatment ordinarily is indicated in these cases, rather than in those involving a simple anterior wall ulcer.

There may be penetration of a jejunal ulcer, and this will involve the transverse colon. In Figure 5 is shown adherence of a jejunal ulcer to the site of a gastrojejunostomy. When evidence of colon irritability develops after a gastric operation, one should always think of a jejunal ulcer with involvement of the transverse colon, and the patient should be operated on

*Gordon-Taylor, G.: Present position of surgery in treatment of bleeding peptic ulcer (Lettsomian lecture). Brit. J. Surg. 33:336-345 (April) 1946.

FIGURE 1. Jejunal ulcer niche, indicated by arrow, occurred following posterior gastroenterostomy.

FIGURE 2. Insufficient gastric resection. Most of the stomach is intact. The patient had three operations; now has large jejunal ulcer along the greater curvature.

immediately in order to prevent this serious complication of the penetration into the colon—fistula formation.

The mortality rate for operative treatment of gastrojejunocolic fistulas is much lower than it was in the past. Before Pfeiffer suggested the utilization of a proximal colostomy, the mortality for colic fistula was from 50 to 60 per cent; today it should be approximately 5 per cent, or even less. This decrease in mortality has resulted because the bowel can be sterilized with antibiotics, and insoluble sulfonamides can be used. In many of these cases the colostomy can be disconnected and the normal gastrointestinal continuity restored.

The only difficulty in this type of restoration is that, although the mortality will be less, the ulcer may again be reactivated and the duodenal ulcer will require a partial resection. On the other hand, this is a safe procedure and the mortality has been markedly reduced. If we will keep in mind that when an individual who has had a gastric operation develops pain in his epigastrium and pain to the left of the costal margin, to the left of the midline, he probably has a jejunal ulcer and in all probability will have to have more surgical treatment.

What type of operation shall we do for these people? Shall we do vagotomies or more resections? As illustrated in Figure 2, most of these jejunal ulcers which appear following gastric resections occur when not enough stomach has been removed. Ordinarily, if the gastric phase of secretion has not been reduced sufficiently, then another resection should be done, and I would have no objection to adding vagotomy to the second resection.

Certain patients have a recurrence of ulcer regardless of the treatment given. Figure 6 demonstrates a case in which only a small remnant of the stomach is left. This patient had had two gastric resections, and after each resection a jejunal ulcer promptly developed. He finally came to the clinic because of hemorrhage, and he was exsanguinated. In going over his record we assumed that in all probability the antrum was still in place. This man required morphine for the relief of his pain.

At laparotomy, only the antrum was removed. Figure 6b is a second roentgenogram taken about six weeks later which shows healing of the ulcer. After operation, this patient did not require any opiate for the relief of pain.

This observation is not new. Von Haberer reported it as early as 1921, but it is a good thing to remember. We never do an exclusion operation any more.

If we find, then, that a patient has had an inadequate resection, we do another resection and perhaps add vagotomy to it. If at least 70 per cent of the stomach has been resected, it is possible to do a vagotomy, but unfortunately that will not protect all these patients. Figure 7 illustrates such a case. This man had no difficul-

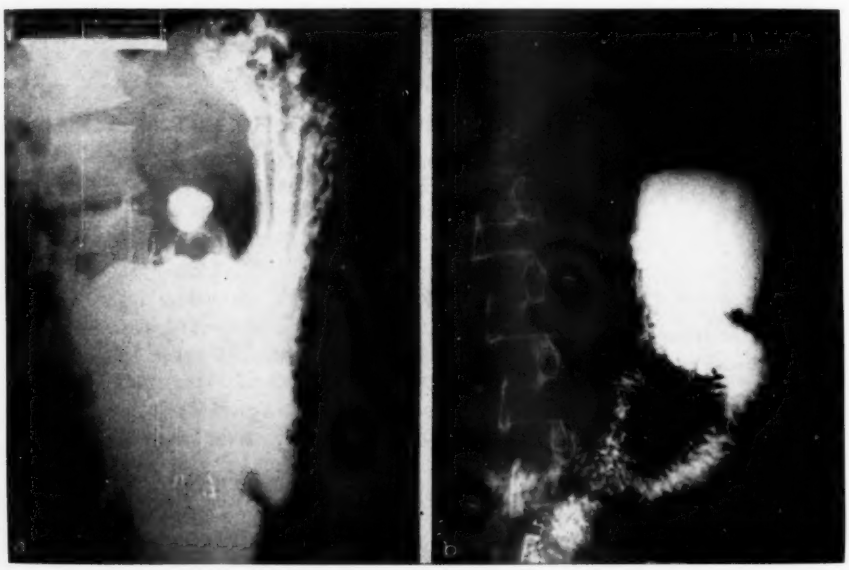

FIGURE 3. Gastric resection for duodenal ulcer. a. Stomach is shown with duodenal ulcer prior to operation. b. Resected stomach; about 25 per cent of the stomach remains after surgery.

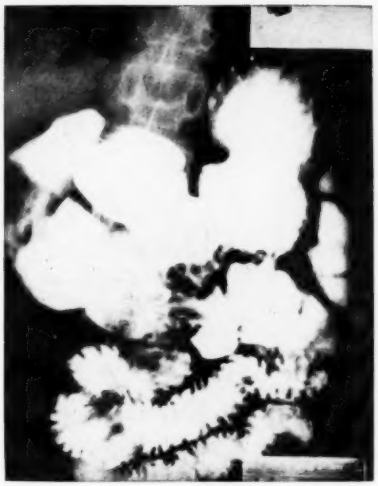

FIGURE 4 *(left)*. Gastrojejunocolic fistula. Roentgenogram taken after a barium meal. Barium fills the stomach and flows into the colon through the fistula.

FIGURE 5 *(right)*. Roentgenogram following a barium meal and barium enema. Colon is adherent at the site of the jejunal ulcer (arrow); perforation into the colon is probable with resulting formation of a fistula.

ty emptying his stomach through the gastroenterostomy stoma, but he had pain. He had had a high resection, a sufficient resection, and it was thought wise to do a transthoracic vagotomy. Within five days after transthoracic vagotomy, the intestine was obstructed. Figure 7 shows the barium pouring out of the pyloric opening into the duodenum, but it does not go past the region of the gastroenterostomy stoma.

It was necessary to do an enteroenterostomy (Figure 7b) in this case to relieve the symptoms. Figure 8 shows the barium entering the jejunum. This patient was in the late sixties; vagotomy was justified in this case, because the patient has been well since the operation.

Table 1 shows some of the results of the collected cases of the Committee on Surgical Procedures of the American Gastroenterological Society. Perhaps some of you have seen the volume on peptic ulcer by Sandweiss.* The results of this study show that in patients with jejunal ulcer only 59.1 per cent were relieved of their ulcer symptoms by vagotomy, whereas 81.4 per cent were relieved by gastric resection. In the group with hemorrhage, which was the chief indication for operation, 61.6 per cent were relieved of their symptoms by vagotomy, and 86.1 per cent by gastric resection. I think this difference is related in the majority of cases to an insufficiently high resection.

Figure 9 shows a definite gastric ulcer on the lesser curvature, and this is where most of them occur. Gastric ulcers are fairly frequent—perhaps not so frequent as duodenal ulcers, but they occur in a ratio of about 1 to 10. The important factor about gastric ulcers is the difficulty in determining whether these lesions are benign or malignant. Unfortunately, the age of the individual, the location and the duration of the lesion do not help in this determination. The size of the ulcer has not been of great help either. I can show you evidence of large benign ulcers in the prepyloric area. We have been told that ulcerations in the antral area are particu-

TABLE 1

GASTROJEJUNAL ULCER: RESULTS ACCORDING TO COMBINED CRITERIA*

	GOOD RESULTS *Per cent*
Without Previous Hemorrhage	
Vagotomy alone	59.1
Gastric resection alone	81.4
With Previous Hemorrhage	
Vagotomy alone	61.6
Gastric resection alone	86.1

*From JORDAN, S. M.: Present status of vagotomy. In: SANDWEISS, D. J.: Peptic ulcer. Philadelphia, W. B. Saunders Company, 1951, p. 544.

*SANDWEISS, DAVID J.: Peptic Ulcer. Philadelphia, W. B. Saunders Company, 1951.

larly dangerous because they are likely to be malignant.

The location of the ulcer has little bearing on whether the ulcer is benign or malignant, except with possibly one type of ulcer that occurs on the greater curvature. Figure 10 illustrates this type. We always operate on any patient with an ulcer involving the greater curvature because almost 100 per cent of them have proved to be malignant.

How can we determine whether a gastric ulcer is malignant or benign? At the present time, when so much emphasis is placed on early recognition and treatment of cancer, it is important that we make the diagnosis early. The survival rate following surgical treatment in cancer of the stomach is the lowest of any malignancy.

In the early diagnosis of gastric carcinoma, we should note particularly whether the individual has achlorhydria, a history of gastric carcinoma in the family or a history of pernicious anemia. We should try to distinguish between a benign and a malignant ulcer. We should pay attention to benign polyps of the stomach and, of course, to so-called atrophic gastritis involving the antral area of the stomach. It is evident that, if these patients are to be operated on early so that the survival rate for cancer of the stomach is to be improved, we must make this diagnosis early. The only way

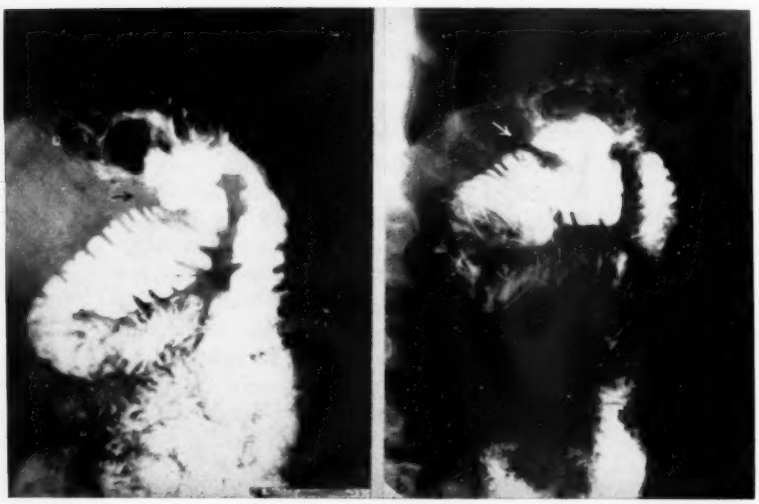

FIGURE 6a. High resection of stomach with jejunal ulcer; operation consisted of removal of retained antrum only. b. Six weeks after operation; ulcer is healed and the patient comfortable.

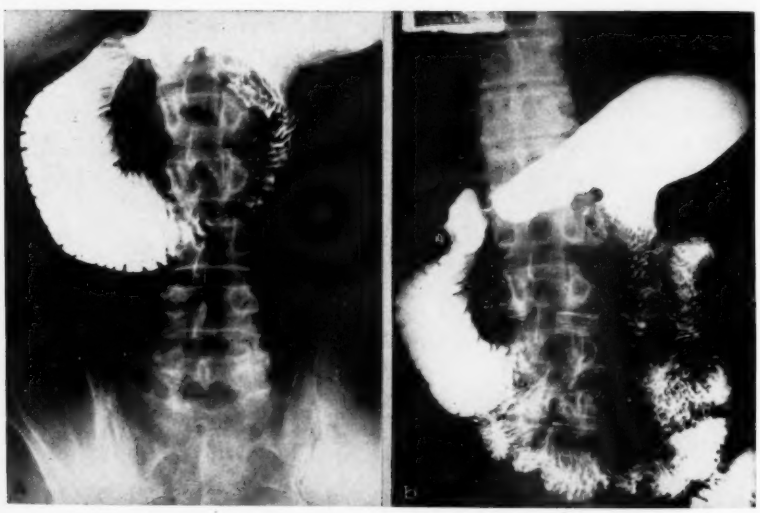

FIGURE 7. Vagotomy for jejunal ulcer after gastroenterostomy. a. After vagotomy, obstruction of jejunal loop occurred at the gastrojejunostomy stoma. b. Obstruction has been relieved by enteroenterostomy.

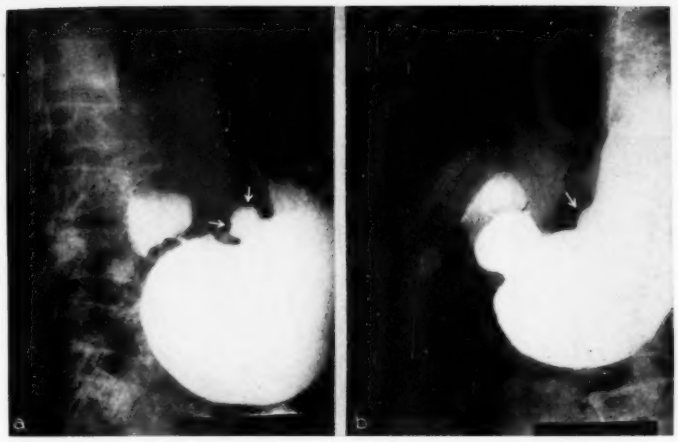

FIGURE 8a. Large gastric ulcer of the lesser curvature. b. Eighteen days after medical treatment in hospital. The ulcer niche on lesser curvature was much less prominent, and operation was not indicated.

that I know to select the patients who should come to surgery is to put them in the hospital and treat them. Figure 8 (a and b) shows a large gastric ulcer on the lesser curvature. The meniscus sign, the size of the ulcer and the location do not help. This patient was hospitalized and given careful treatment. About 10 days or two weeks later the ulcer was measurably reduced in size. The ulcer niche should disappear entirely and should not recur, and occult blood in the stool should disappear. If the patient fulfills these requirements we are justified in not operating.

Figure 9 shows a small ulcer on the lesser curvature. The patient was a girl 19 years of age. She was treated for a period of 10 days and there was no change in the appearance of the ulcer. Resection was performed and carcinoma simplex was found. She died one and a half years later.

Figure 10 shows an ulcer on the greater curvature. This is the type of case in which we always operate. The penetration can be seen in the lateral view. The tendency to penetrate is characteristic of ulcer. The patient, a man 68 years of age, had achlorhydria. Resection was performed and a benign ulcer was found. This was the fifth case of benign ulcer of the greater curvature which we have seen at the clinic since this man left the hospital. Recently I sent home a 34 year old doctor with an antral lesion on the greater curvature. He had come to the clinic with a diagnosis of carcinoma and had been operated on immediately. He constituted the sixth case of benign ulcer on the greater curvature, so you see how rare it is.

Figure 11 is the resected specimen of the ulcer

FIGURE 9. Malignant ulcer of lesser curvature of stomach in a 19 year old woman.

shown in Figure 10. The ulcer can be seen in the midportion of the stomach involving the greater curvature. Operation is the only means by which we can determine whether these ulcers are benign or malignant. The incidence of error is entirely too high to treat the average gastric ulcer patient for a long period of time.

Dr. S. M. Jordan studied 600 cases of gastric ulcer treated medically and surgically, of which 270 came to operation because of persistence, recurrence or because of difficulty in making the distinction between benignancy and

FIGURE 10. Benign ulcer on the greater curvature of the stomach in a 68 year old man, proved by operation.

FIGURE 11. Resected portion of stomach of a 68 year old man. Ulcer on the greater curvature was benign (see Figure 10).

malignancy. Fifty-nine proved to be malignant ulcers—an incidence of 21.7 per cent.

If the entire group is considered, the incidence of error is approximately 10 per cent. Therefore, it is extremely important to select these cases, to prove that the ulcers are not malignant and to operate on these patients early if the incidence of gastric carcinoma is to be decreased.

The problem of surgical treatment for peptic ulcer can be clearly settled. We know the indications for operation. In other words, the patients who have failed to respond to medical treatment should be operated on. Unfortunately, the mortality rate for operative procedures for peptic ulcer may be related in a few instances to the delay in bringing these individuals to surgery. The mortality rate for gastric surgery is associated with the large posterior wall lesion that penetrates the duodenum and involves the common duct and surrounding structures. If we could see these patients immediately after failure of medical management and before they have gone through 10 or 15 episodes of failure, I am sure that many of them could have resections in time to reduce the risk.

It is well to point out that vagotomy is a valuable procedure only as an adjunct and to remember that there are three phases of gastric secretion. The first is the gastric phase, which can be controlled with a gastric resection. That means that if a high gastric resection—removing at least 70 per cent of the stomach—has been done, we have done all we can to control the gastric phase. The second phase is the cephalic phase, and vagotomy can be used to control this phase. The third phase is the intestinal phase. So far we have nothing with which to control the intestinal phase of gastric secretion. If the gastric acid can be reduced, a tremendous amount can be done for patients who fail under medical measures. Certainly in our experience and in our judgment, we are still placing most of our reliance for the treatment of the failures of medical management on the operative procedure of partial gastrectomy.

Frigidity in Women

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The incidence of frigidity in women is much higher than most physicians realize. The treatment of this affliction is both prophylactic and curative. Most women with true frigidity must be treated by formal psychiatry, but many can be helped considerably by an understanding and sympathetic physician.

J. P. GREENHILL

THE subject of frigidity in women is of considerable interest to gynecologists, psychiatrists and psychoanalysts, but the general practitioner must also familiarize himself with this distressing cause of unhappiness. Bergler[1] maintains that frigidity is a problem which concerns from 70 to 80 per cent of all women. In my experience the incidence is not this high, but surely more than one-third of all women fail to enjoy the pleasures of sexual intercourse. Bergler believes that nine-tenths of all cases of infidelity on the part of the woman are traceable to frigidity. You must agree, therefore, that frigidity is important not only from a medical and a psychiatric point of view but also from sociologic and moral standpoints.

True frigidity must be differentiated from dyspareunia and pseudofrigidity. Dyspareunia signifies difficult or painful sexual intercourse. It nearly always involves vaginismus or spasm of the muscles surrounding the vagina and in most instances there is a large psychic factor. Vaginismus may occur without dyspareunia, as for example during a vaginal examination.

Pseudofrigidity has many causes. Common ones are fear of pregnancy—even with the use of contraceptives—and pain from a too tight perineal repair. The frigidity usually arises soon after a baby is born, particularly if the labor was hard and prolonged. The immediate postpartum period is often a very trying one with a new baby in the home. When coitus is resumed after a baby is born the wife frequently associates sexual intercourse with the cause of her pain, fatigue, anxiety and loss of freedom. This condition is called postpartum frigidity.

Other causes of pseudofrigidity are impotence of the husband, premature ejaculation, intracrural intercourse, clumsiness, ignorance of the proper technic on the part of the husband, misunderstandings, quarreling and ill health.

True Frigidity

According to Bergler,[1] there are four theories to explain frigidity in women. The first concerns the culturally determined rejection of sex; frigidity may represent the behavior of the overly moral and cultured woman; it may be characteristic of the "respectable" woman to feel no

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sexual pleasure, to reject everything sexual as indecent, or at best to submit but passively to the male. The second theory concerns the woman who can be aroused, but who cannot experience an orgasm. The third theory deals in general terms with the extent and location of the emotional satisfaction of the woman in coitus. This is the "clitoric theory," according to which sexuality is masturbation *a deux* and it does not matter how and when the woman derives gratification—before, during or after coitus. The fourth theory, the "vaginal," defines frigidity as the total incapacity for vaginal orgasm.

According to most psychiatrists, the confusion over what constitutes frigidity arises from the lack of knowledge that true frigidity is based on the supposition that the psychosexual factors in feminine maturation actually involve two organs—the clitoris and the vagina. The clitoris plays the dominant role in the masturbatory habits of the child as well as of the emotionally infantile adult. The clitoris is the more easily discovered part of the female genitals and the one which first yields the most pleasure when stimulated. Therefore in childhood all the attention is usually focused on the clitoris, resulting in little vaginal excitation. In women fixed at the clitoric level of development there is a complete lack of pleasurable vaginal sensitivity to stimulation. This is the result of the unconscious denial of the vagina and concentration on pleasure from clitoric stimulation. The vagina is psychologically unimportant until puberty; hence in the child the clitoris gives sexual satisfaction whereas in the emotionally mature woman the vagina is supposed to be the principal sexual organ. In frigid women the transference of sexual satisfaction and excitement from the clitoris to the vagina, which usually occurs with emotional maturation, does not take place.

The vaginal anesthesia which is present in many frigid women probably represents an inner denial of the "normal" pleasurable sensations derived from intercourse. To these women the husband may still unconsciously symbolize the father and, therefore, sexual intercourse with him is not allowed to yield pleasurable sensations. Since sexual desires for the father were forbidden, then sexual pleasure with the husband—who is unconsciously identified with the father—is impossible. Frigidity may be due to fear of punishment for violating sexual prohibitions, to conflicting loves, to love of father as opposed to love of husband, to love of self as contrasted to love of husband, and to love of other women as opposed to love of men, represented by the husband. Unconscious resentment and hostility with a wish for revenge on men, based on the castration complex, or a wish to avenge the mother for all the suffering she went through at the hands of the father may lead to real frigidity. Hence the reactions of the envy of men and the fear of damage to genital organs play at least some part in the psychosexual maturation of every girl and in many cases they are the dominating factors in the development of the psychopathology responsible for the symptom complex of frigidity.

Diagnosis

How can a physician attempt to determine whether or not true frigidity is present? If a physical examination of both husband and wife reveals no structural reasons for frigidity one may safely assume that emotional problems are present which interfere with adequate sexual response. One way of attempting to make a diagnosis is to question the husband concerning the wife's response to coitus. A physician may point out to the husband that there is only one matter in which the wife is completely helpless, namely, controlling the involuntary contractions of the pelvic and perineal muscles which occur at the end of the coital act. This is the sole criterion for determining the presence or absence of orgasm. A woman has absolutely no conscious control over the muscles involved in these involuntary contractions. The husband may feel these fine fibrillary contractions which usually culminate a gratifying sexual experience. Any attempt at simulation is impossible, providing, of course, that he knows how to detect it.

Another indication, though less reliable, is the absence of lubrication at the entrance of the vagina before and during coitus. This is only a presumptive sign of frigidity. Of course, the reverse is not true; the presence of adequate

secretion does not exclude the presence of some form of frigidity. Many women may have a leukorrheal discharge that may be mistaken for glandular secretions. It should be easy for a physician to diagnose pseudofrigidity which results from impotence on the part of the husband, lack of proper technic, premature ejaculation, coitus interruptus and intracrural coitus. This information can be obtained by questioning both husband and wife.

Treatment—Prophylaxis

Until recent years it was almost a universal custom for parents to try to keep their young sons and daughters in ignorance about sex matters. It was assumed that boys in their later teens would learn about sexual intercourse by practical experience. This was true in most instances, but many boys paid a heavy penalty by acquiring venereal disease because they had not been warned of the dangers of promiscuous sexual intercourse. On the other hand it was taken for granted that all girls would remain virgins until they married and that their husbands would instruct them in all sex matters. However, many girls, just as most boys, learn a good deal about sex not only from secret discussions with older friends but also from practical experience before they marry.

Every physician knows of the many dire consequences which have resulted from not educating children about sex matters. An enormous amount of marital unhappiness and ailing among women stems from total ignorance concerning the human organs of reproduction and the mechanics, art and psychology of sexual intercourse among human beings. Additional factors are repeated admonitions of parents to their young daughters to repress all sexual impulses and to look askance at all men who attempt to demonstrate their affection by physical means, such as petting.

Many states now have laws which require that shortly before marriage both partners present evidence of the absence of venereal disease. This is highly commendable, but it does not go far enough. In addition to this, prospective brides and bridegrooms should be given instruction not only in contraception, about which most young couples voluntarily seek advice or already have some knowledge, but also in the psychology and technic of sexual intercourse. This applies just as much to the groom as to the bride because, even though the young man may have had sexual experiences for many years, he must be made aware of the fact that physical relationship with his virgin bride requires an entirely different technic from that which he employed with prostitutes and chance acquaintances who helped him satisfy his carnal desires for some reason or another but seldom for love.

The ideal arrangement is for every prospective bride and groom to interview a physician—preferably the family physician, whom they know well. First the girl should be seen and then the young man; then, if necessary, they should be seen together after the individual interviews. Mass instruction such as is given in some colleges is excellent, but for the practical preparation for marriage just before the latter is to take place, nothing can be compared with a direct person-to-person conference in private.

Such a conference should consist of three parts—a physical examination, instruction in the art of sexual intercourse and advice about the prevention of conception. This meeting between the physician and the young couple should take place about two weeks before the wedding. The talk should be as informal as possible, and the physician should not write down any part of the history in the presence of the bride-to-be. He should inquire first about the girl's general health and then about her past history, especially concerning the onset of the menses and any difficulties connected with the menstruation. Then he should try to find out whether the girl has any fears concerning marriage, the sex act or childbearing. He must constantly attempt to allay any fear the girl has concerning these matters by giving rational explanations. During the conversation the physician usually obtains a good idea of whether the girl was brought up as a prude to repress all matters pertaining to sex or whether her parents educated her in an enlightened manner. This information will usually lead in a natural manner to a discussion of the anatomy and the physiology of the genitals. For instruction along these lines

it is necessary to produce illustrations or, better still, a model of the external and internal pelvic organs such as is used for demonstrating the insertion of a contraceptive vaginal diaphragm. All the organs are pointed out and the function of each one is described in simple language. Then a physical examination should be made.[2]

Knight[4] made the following recommendations to parents and educators concerning the prophylaxis of frigidity:

"1. In general, a home atmosphere characterized by security, affection and tolerance, absence of parental disagreement before the children and consistent giving of affection and enforcing of discipline by both parents to all the children constitutes good prophylaxis against all later emotional and psychosexual disorders.

"2. It is particularly important that parents and older siblings do nothing to influence a child of one sex toward behavior and feelings appropriate to the other sex. When the parents have wanted a boy, for example, and instead a girl is born, it is essential that the girl not be apprised of the parental hopes and regrets in this regard. Also, she should be permitted and encouraged to be normally feminine and not be 'processed' into a tomboy because they would have preferred a boy.

"3. No matter how difficult the delivery of this girl was (or that of any of the other children) or how near death the mother was during or after childbirth, this story of suffering and miraculous escape from death should never be related to the little girl.

"4. The parents, especially the mother, should take a practical, unembarrassed attitude toward matters of bathing, toilet training, childhood masturbation or childhood sexual exposures and experimentation with playmates, so that prudery is not furthered. Parental indignation, intimidation and severe punishment for childhood sexual manifestations many times do more harm than do the experiences themselves.

"5. It is probably desirable that children of both sexes be permitted to play about naked and bathe before each other during the first 8 or 10 years, but childhood observation of the parent of the opposite sex in the nude or during excretory activities has a harmful psychologic effect.

"6. Children should, if at all possible, sleep alone in rooms of their own. It is always deleterious psychologically for children to sleep in the same bed or same room with the parents, and especially to observe or overhear parental coitus.

"7. Unembarrassed explanations and preparation for the menarche before it happens should always be made by the mother.

"8. Education of the little girl toward chastity can easily be overdone. Repeated warnings against boys and men as nasty, cruel beasts constantly seeking to take advantage of and ruin girls and women are much worse than no education at all.

"9. Children's sexual curiosity expressed in questions should always be answered fully and correctly. Children pay more attention to the tone of voice and attitude of the parents doing the explaining than they do toward the information itself."

Treatment—Curative

The consequences of frigidity are often tragic for women. They lead from dissatisfaction, depression and hysterical symptoms to the most typical defense mechanism, namely, denial by the woman that she is ill and the constant changing of husbands and male friends. Every new affair ends in the same fiasco. Except for psychiatrists and psychoanalysts, the family physician and the obstetrician and gynecologist have a closer relationship with the emotional problems of the patient than does any other type of physician.

Before therapy is attempted, a thorough physical examination should be made, particularly of the pelvic organs. Of course if any physical cause for dyspareunia or frigidity is found it must be removed. Thus if an intact hymen is present it should be ruptured and stretched under general anesthesia, irritating vaginal discharges should be cleared up, caruncles should be removed and a tight perineum stretched digitally under anesthesia or widened by a perineoplasty.

In nearly all cases of dyspareunia and pseudofrigidity it is advisable to have a conference with the patient's husband. Much may be learn-

ed from this talk, but it is important for the physician to enlist the husband's cooperation in helping to overcome the wife's ailment. In many cases of dyspareunia the husband loses patience and becomes angry, and discord arises. This increases with each attempt at coitus and unless someone, such as a physician, interferes early, a serious marital rift occurs. Therefore it is essential to discuss the situation with the husband soon after the patient's first visit.

If the physical examination fails to reveal any abnormalities and provided the patient has in the past experienced pleasurable sensations from coitus, the male hormone, testosterone, will give satisfactory results in about 75 per cent of properly selected cases. A satisfactory method of stimulating or increasing sexual desire is to administer 25 mg. of testosterone propionate hypodermically three times a week for two weeks and 25 mg. twice a week for two more weeks. After this the patient should use 5 mg. of the androgen sublingually every second day for four weeks. After stopping two weeks, the sublingual treatment should be used for another four weeks. The resulting enlargement of the clitoris undoubtedly plays an important part in stimulating libido. In most cases the effect is long-lasting, most likely because the psyche is aroused.[3]

While male hormone therapy is generally successful in women who have experienced orgasms and later have become frigid, it does not often arouse sex desire in women who have always been frigid. Patients who are treated for frigidity with androgens must be warned about the dangers of virilism, because the signs of virilism will surely add to their unhappiness, especially if the treatment is a failure or the patient is vain. No patient should be urged to undergo androgen therapy for frigidity if she does not desire it. Bergler maintains that a typically frigid woman suffers not from a deficiency in libido but from a neurosis, that is, an illness of the unconscious. For this reason hormone therapy is unsuccessful in cases of true frigidity.

Since the problem of frigidity is predominantly emotional rather than somatic, some may question the right of anyone but a psychiatrist or psychoanalyst to treat women with frigidity. It is true that most women with frigidity should be treated by formal psychiatry or psychoanalysis, but many frigid women—particularly those who are not too emotionally unbalanced—can be helped considerably by an understanding and sympathetic physician.

As Kroger and Freed[5] point out, psychoanalysis—while often successful—is expensive, time-consuming and requires extensive technical training on the part of the therapist. On the other hand, superficial psychotherapy may be of particular value in treating pseudofrigidity.

One type of conflict is based on a lack of satisfaction with resulting tension when women fail to receive gratification from their early coital attempts. All that some women need is encouragement and the knowledge that sexual gratification consists of variable responses and may eventually be achieved. Kroger and Freed emphasize that failure to attain this satisfaction often creates a feeling of inadequacy. The patient becomes fearful, feels inferior and thus a vicious cycle is established which may become irreversible unless the patient receives wise counsel and encouragement from the physician. It may help these patients to tell them that a gratifying sexual life is rarely the result of the first few attempts.

In some women pseudofrigidity is present even though they experience acute sexual arousal. They are only temporarily inhibited by some situation or circumstance affecting their sexual lives, the correction of which leaves them free to establish or re-establish a pattern of gratification. Frequently the patient is handicapped by her faulty attitude toward her difficulties. Having begun her act of sexual life only to meet disappointment and frustration—the reasons for which are more or less obscure to her—time confirms her disappointment and she tends to assume an attitude of indifference which soon gives way to hostility and resentment. She acquires an attitude of defeat, looks for escape consciously or unconsciously, and is tormented by feelings of inferiority and guilt. These women are the ones who are desperately in need of help, perhaps more so than the truly frigid woman, for they have some idea of what they are missing in the emotional fulfillment of their lives. These are the persons whom the family

physician or the gynecologist may be able to help if he succeeds in discovering the essential elements of their problems.

Conflict may be caused by the atmosphere and environment in which sexual intercourse occurs. The woman may lack a feeling of complete security. Inadequate housing which causes a couple to live with parents may produce more than the ordinary personal conflict resulting from two families living under one roof. The self consciousness and guilt associated with the sexual activities of two young people living their sexual lives under the eyes and within the hearing of the parents is almost inevitable, for these same parents have often, by means of taboos and threats, sought to control the early sexual drives of their children. The mere legal sanction of marriage is not sufficient to allay or completely change their attitudes. No matter how trivial these factors may seem to the husband or physician, if their correction cures the pseudofrigidity they are obviously important.

Personal habits may provide another source of conflict. If the partner is not fastidious in the care of his person—by taking too few baths and poor care of the teeth, for example—the woman may feel disgust and be unable to participate freely and happily in intercourse. The husband may wish to indulge in certain types of sexual play which the woman feels are abnormal. She may feel offended by his desire to experiment with what she considers abnormal postures for intercourse. The husband may have a deep need for gratifying a desire to see his partner in the nude and may want some light in the room whereas the wife's sense of modesty and decorum may be offended by these procedures with resulting inhibition of all sexual pleasures. All or any of these conflicts may be indicative of neurotic personality patterns but they are not necessarily permanent and may be corrected by proper education. Some minor conditions which may easily be corrected are lack of pleasure from coitus interruptus, intracrural intercourse, and a real or imagined difference in the size of the penis in the vagina. In nearly all cases where a woman says the penis is too large or too small it will be found that faulty attitude and incorrect technics are responsible for the lack of pleasure. In rare cases the vagina is actually too large or the muscles are too lax for a woman to perceive and feel the penis properly in the vagina. In such cases a plastic operation will eliminate the source of trouble, but these cases are rare.

An understanding of the psychodynamics of frigidity will enable a physician to treat it more adequately. The important thing about therapy is that the unconscious conflicts which have produced frigidity must be made conscious, and this can be most effectively accomplished through adequate analytic interpretation and subsequent insight.

According to Reynolds,[6] the important dynamics as they relate to true frigidity are as follows:

1. Guilt feelings because of infidelity on the part of the patient may often result in frigidity. She may be in love with another man or may merely feel a sexual attraction toward other men. As a result, her guilty conscience may cause her to be inhibited with her husband, or she may think he is unfaithful to her, and the resulting hostility toward him will, by itself, produce frigidity. The frigid women in this group are unable to react "normally" in the sexual relationship for reasons of which they are totally unaware. Thus the ordinary approach of discussion and re-education is useless. These are the persons who must be referred to the analytically oriented psychiatrist.

2. Since religion and/or morality assume prominent roles in the etiology of true frigidity, considerable emotional reorientation will be necessary to overcome their ill effects. Morality has been used to restrain and control illicit sexual relations to such an extent that, to many minds, all sexual relations are impure and taboo.

3. Psychoanalysis explains the Oedipus complex as an arrested emotional development at the level of childhood when the love object is the parent of the opposite sex. Thus the woman with such an arrested development in her emotional life tends to seek a husband who approximates as nearly as possible the image of her father. Unfortunately the sexual relationship connotes incest and reactivates earlier oedipal anxieties, thus producing a severe conflict, guilt and total frigidity.

4. Hostility toward all men is a factor fre-

quently found. Many women are unconsciously envious of the male role and resent man's domination and so-called superiority. This accounts for the "masculine protest," based on their envy of the penis and castration complex. The frigidity of these women is a protest against submission and the giving of pleasure and satisfaction to the male. Also, with such women, marriage merely satisfies the needs of narcissism or too much self love.

5. Latent homosexuality may be another factor. This condition is present much more frequently than was formerly recognized.

6. Narcissism may be still another factor. A degree of self love is necessary to establish self respect. Normally, love for another person is an overflow from self love. In the narcissistic person there is no love left over for the sexual partner, with resulting frigidity.

7. The emotionally immature woman is usually frigid. She still clings to her childhood dependency state and, since sexual maturity definitely denotes an adult role, it is impossible for her to attain sexual satisfaction. In reality she is still at the doll-playing stage of emotional development and as a consequence is a poor sexual partner or mother.

In closing may I point out that the treatment of these women is a difficult, tedious and expensive procedure which must be carried out by an expert. General practitioners, obstetricians and gynecologists must know their limitations in the field of psychotherapy lest they do more harm than good.

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I am grateful to Drs. W. S. Kroger and S. C. Freed for the use of material from their book, "Psychosomatic Gynecology." I wrote a foreword for this book because for many years I have discussed psychotherapy in gynecology with the authors.

NEW BOOKS RECEIVED

Vascular Diseases in Clinical Practice. By Irving S. Wright, M.D., Cornell University Medical College, New York City. Ed. 2. 552 pages with 116 figures. 1952, The Year Book Publishers, Inc., Chicago. $8.50.

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The Cumulative Effects of X-Ray Exposures

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Widespread public interest in nuclear fission has revived concern about the deleterious effects of x-rays and radium. Some of the concern is sound, some quite unjustified. Sharp distinction must always be made between the small doses employed in x-ray diagnosis and the large doses required in therapy; in either instance radiation should be employed only if it is really necessary.

FRACTURES that fail to unite are inconvenient for the patient and embarrassing for the physician, so it is not surprising that, in cases of nonunion, physicians are inclined to blame factors beyond their control. Some decades ago the suggestion was made that excessive diagnostic raying might be blamed for some cases of nonunion, but this theory was not supported by animal experiments. On the contrary, experiments indicated that the x-ray doses required to interfere with the union of fractures were large even by the standards of therapy and enormously greater than the largest doses that ever would be delivered in connection with x-ray examinations.[1,2]

I had supposed that the fallacy had been forgotten and that diagnostic raying had been deleted from the lists of possible causes of nonunion of fractures, but your Program Committee has asked me to deliver still another blow to the ancient myth.

In the past 15 years workers at the University of Michigan,[3,4] the University of Iowa[5] and elsewhere have been reporting the occurrence of fractures of the femoral neck in a small percentage of their patients who have received heavy irradiation for neoplasm, usually of the uterus. Some of these fractures occurred less than a year after treatment, others not until almost four years had elapsed, but in all of them it seemed clear that the lesion was caused by intense irradiation of the bone rather than by trauma or by spread of the neoplasm. Some of the earlier observers in the group believed that the fractures showed less than the normal tendency to unite, but agreement is now general that when they are treated like ordinary fractures[6] they respond like them.[7] If such pathologic fractures caused by enormous therapeutic doses of x-rays will unite when they are properly reduced and properly immobilized, it must follow that overzealous fluoroscopy and radiography of traumatic fractures, which at worst involve relatively small doses, can scarcely be responsible if subsequently those fractures fail to unite.

In addition to discussing the cumulative effects of x-ray exposures, I will consider exposures to other forms of ionizing radiation as well, because biologically and physically all these forms, including x-rays, constitute a

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continuous system. On the other hand, I shall speak only of a few of the known effects of ionizing radiation and of necessity omit many other effects. Since the doses used in diagnosis compare with those employed in therapy about as the heat of a match compares with the heat from a blow torch, I shall take pains to distinguish sharply between the risks of diagnostic raying and those of therapeutic raying. I shall attempt also to consider separately the deleterious effects on the individual receiving the radiation and the possible effects on his descendants. This latter genetic aspect of the problem will involve extrapolation from actual observations on short-lived laboratory material, such as fruit flies, and thus will get us into the question of the nature of evidence and the uses of true logic versus the pitfalls of false logic.[8,9]

Indications for Radiation Procedures

Bear in mind that ionization is injurious to living tissue. When the dose is small or is spread over a long period of time, the injury may be detectable only with difficulty and only after the lapse of considerable time. When large doses are delivered in comparatively short periods of time, however, the deleterious effects to the tissues become demonstrable within days or even hours; in either case the subject experiences little or no immediate sensation. Some tissues are relatively resistant to radiation, others are extremely sensitive, but none are immune. The damage increases with the dose per unit of volume and also with the total volume irradiated. It is the absorbed dose that is significant, and the wavelength of the radiation plays a role only as it affects penetration and absorption.

If these facts are true, why then do we employ roentgen rays at all and why is Roentgen's discovery deemed a blessing rather than a curse? The cutting, cauterizing and scraping of tissue certainly cause damage, but properly conceived and skillfully executed surgery may be a lifesaving procedure. Many important drugs are tissue poisons, but when wisely used they are indispensable in the fight against disease. Roentgen rays, radium rays and the other ionizing agents are dangerous, it is true; but when they are used with skill and discretion they do more good than harm. The harm is always there, however, and it is our obligation as physicians to keep it always in mind.

To argue that a particular therapeutic or diagnostic procedure can do no harm—and, therefore, is justifiable even though it may not reasonably be expected to do any good—is bad on general principles. When the procedure in question involves ionizing radiations, it is bad for the additional reason that it is untrue. The harm is there invariably and the best policy is to employ radiation only when less dangerous agents are clearly inferior. In therapy this means employing it only for those cases of neoplasm in which surgery offers less in terms of function or survival. In diagnosis it means first the avoidance of repeated examinations unless the need for them is real, and second the avoidance of x-ray examinations altogether in regions and organs where the palpating finger or the endoscope will do an even better job.

TABLE 1

APPROXIMATE AMOUNTS OF RADIATION REQUIRED IN DIAGNOSTIC RADIOLOGY

Stereoscopic chest films of an adult:	
Skin dose	0.1 r
Depth dose	0.02 r
Pelvimetry on the maternal pelvis at term; frontal and lateral films:	
Skin dose	35.5 r
Depth dose	2.6 r
Complete colon examination, including fluoroscopy and films:	
Skin dose	73 r
Depth dose	15 r
Complete stomach examination, including fluoroscopy and films:	
Skin dose	97 r
Depth dose	20 r

Amount of Radiation Required

If all these policies were followed everywhere, there would still remain enough necessary and therefore justifiable therapeutic and diagnostic radiology to keep all radiologists

busier than they ought to be. Internists, surgeons, general practitioners, etc., have the responsibility of deciding which patients are to be sent to us, and we radiologists have the responsibility of assuring that the tissues of those patients, the tissues of our technical helpers and the tissues of our own bodies receive only the amount of radiation that is absolutely essential to the task in question. This irreducible amount will vary widely from case to case. In diagnosis we do not customarily measure and record doses, but the values run approximately as shown in Table 1. In therapy the tissue dose may be as small as 1200 r in some lymphomas and as much as 5000 r in most laryngeal carcinomas.

Risks of Diagnostic Raying

In diagnosis we continue to find means of decreasing the tissue doses necessary for the production of films and fluoroscopic images, but this potential reduction in exposure is more than counterbalanced by a seemingly endless increase in requests for more and more fluoroscopy, the making of more conventional films during each examination and the employment of more laminography, photofluorography, x-ray motion pictures, angiography and similar multiple film procedures. The old rule of thumb that once sufficed as a safeguard no longer is safe. By that crude rule we believed that if radiation caused no detectable changes in the skin of a part no significant changes would follow in the underlying tissue. It was a useful rule for patients because for them exposure to diagnostic rays was an acute, infrequent affair; but we recognized that different rules were necessary for workers chronically exposed to radiation or for anyone subjected to irradiation of the entire body. Today patients are so apt to undergo repeated x-ray examinations that the problem of their cumulative dosage becomes similar to that for radiologists and x-ray technicians. Even so, the recently published suggestion of a personal diary for each member of the entire population seems to me impractical.[10] I prefer the concept that, whether the previous x-ray dosage absorbed by a patient was large or small, the proper amount to give him is always the same—namely, the smallest amount that is consistent with his present diagnostic needs. Of course I am speaking here merely of diagnosis, because the fact that complete diaries are essential in therapy has long been recognized by radiologists, physicians and many patients. Later on in this discussion I shall tell you of certain technical developments aimed at the reduction of the absorbed dose in fluoroscopy and the making of films.[11]

Risks of Therapeutic Raying

In radiation therapy the doses are now larger than ever but this increase is deliberate and, paradoxically, the patient is safer now than he used to be and less apt than formerly to suffer unfavorable side effects. This has resulted largely through the abolishment of the concept of the "air dose" and the substitution of the concept of the "tissue dose." A skillful and experienced team of physicians and physicists equipped with modern radiologic tools can with safety deliver large and precisely measured doses of radiation to sharply localized blocks of neoplastic tissue and yet spare neighboring structures that are thought to be normal or are known to be essential to the patient's survival. This development is of immeasurable importance to cancer patients but it has wiped out any place there may ever have been for the amateur worker in radiation therapy. I wonder sometimes whether a tacit recognition of this fact may account for the unfortunate increase in the employment of radiation for the treatment of bursitis, arthritis and other nonmalignant diseases. It is true that some qualified therapists do advocate such treatment but I suspect that many of its advocates are physicians who, having invested in therapy equipment, now recognize their inability to deal with neoplasms but hope that the old air dose technics are still sufficiently good for the treatment of nonmalignant conditions.

Genetic Aspects

The science of genetics has come a long way in the four score and five years since Gregor Mendel's work on the heredity of the

peas that grew in his monastery garden. Today genetics ranks with astronomy and physics in its employment of philosophic and mathematic reasoning and in its continual testing of assumptions and deductions by direct laboratory experiments. But here the similarity ends for, instead of telescopes, mass spectrographs and cyclotrons, geneticists employ merely the lowly fruit fly. A little radium and x-ray to cause mutations in his genes, a whiff of ether to quiet him for counting, a low power microscope to aid in that counting, together with tally sheets, graph paper, computing machines, the glass jars in which the fly and his copious progeny live and the mashed banana on which they feed—these constitute the undramatic working tools of the geneticist. Because these tools are not esoteric, the geneticist suffers a disadvantage that does not plague astronomers and physicists. The laity, awed and dumbfounded by the paraphernalia of observatories and physics laboratories, are more apt to accept pronouncements of the astronomers and physicists as infallible, but fruit flies are within anyone's comprehension, it seems, and isn't it silly to postulate a parallel between human genetics and the occurrence or lack of occurrence of red eyes, long legs, or short wings in the offspring of irradiated fruit flies? No, it isn't silly, and the celebrated human geneticist H. J. Muller, in lectures and publications, has developed the logical argument for those who are willing and able to comprehend.

Extrapolation from fruit flies to mice to man must be done cautiously and with the aid of expert statistical analysis of great masses of data, but it can be done. Similar extrapolations are commonplace in the physical sciences, and if they were not employed in biology the genetics of man would remain almost entirely unknown. Irradiation of the human testicle or ovary unquestionably carries the risk of increasing the mutation rate in the germinal tissue, but it is not genetically reasonable to expect that the resulting damage will be revealed by gross anatomic defects in the immediate progeny. Unfortunately, however, many people—including some physicians—do not understand the point and assume that if no monsters are produced no damage has been done. Qualified geneticists point out that even in the immediate descendants of the survivors of the Hiroshima bomb no visible damage is likely to be found. Unquestionably the germ cells of these survivors have been damaged and the gene mutations caused by that damage will take their toll for generations to come, but that toll will be demonstrable only with the passage of time and the application of careful analysis to great masses of data.

It is genetically clear that if the gonads of fertile humans must be given therapeutic doses of radiation the patients thus irradiated should be sterilized. But this is not generally done and, on the contrary, there are physicians who advocate "stimulating" doses to the ovary or the temporary sterilization of males for whom incontinence is distasteful and immediate fatherhood inconvenient. In fatuous defense of such outrageous practices, these physicians point out that among the offspring eventually born to such irradiated patients no monsters and no legless or armless children have been found.

The genetic risk is present in diagnosis as well as in therapy and, as I have pointed out, the aim should be to fluoroscope and film only when necessary and to keep the dose at a minimum throughout the body and particularly in the gonads. Geneticists do not advocate risking the life or social usefulness of an individual by denying him diagnostic raying just because that raying is inimical to his unborn great-grandchildren. What they do urge is that the genetic risk be recognized and kept as small as possible.

Technical Safeguards

Certain technical means are available at present and others are likely to become available in the future whereby we may reduce the risk of damage to the somatic and germinal tissues of patients coming for x-ray diagnosis. Let me emphasize that word "technical" and remind you again that a certain nontechnical safeguard is most important of all—namely, the avoidance of x-ray examinations unless there are sound reasons for doing them.

Fast screens, fast films, high voltages, greater target-film distances, and the sharper conning of the x-ray beam—these approaches long have been known and employed to keep tissue doses at a minimum during the making of x-ray films. Recently Trout and his associates at the General Electric X-Ray Corporation[11] have shown that the insertion of an aluminum filter 3 mm. thick in the x-ray beam has little or no undesirable effect on the resultant film but reduces sharply the dose to the patient's tissues. In fluoroscopy the patient dose may be decreased and the quality of the image improved by thorough dark adaptation of the examiner's eyes, the use of extremely sensitive fluoroscopic screens and employment of radiation beams of the smallest possible cross-section area. In our own gastric fluoroscope, for example, the maximum beam size is 4¼ by 7 inches. It is even more important to train the radiologist to take his foot off the switch whenever he is not actually observing and do his thinking or discussing with the screen dark. Such teaching runs counter to almost everything young physicians are taught about other diagnostic procedures where deliberate thoroughness and repetition are first-order virtues. In filming and fluoroscopy, parsimony must be learned.

Photofluorography or the microfilming of the chest is an important public health measure that properly is being adopted widely. Unfortunately, however, the refractor lenses that are usually employed for this work are rather slow, having speeds of from F 2.0 to F 1.50, and as a result the tissue dose is from 20 to 50 times as great as in the making of ordinary chest films. Filtering the x-ray beam with 3 mm. of aluminum will reduce the dose and a still further reduction can be accomplished by replacing refractor lenses by lens mirror systems of the Schmidt type where the speed may be as great as F 0.75 or F 0.62.

In its present state of perfection, fluoroscopy requires doses to the patient and the examiner that are larger than we like to employ and yields images so faint that the study of them strains our vision to the utmost. When we have learned to amplify that image electronically, all this will change. The radiation dose will fall to a safe level and the image brilliance will become so great that it can be seen with ease and photographed with ordinary cameras. The matter is receiving the vigorous attention of at least four research groups in this country and probably others as well here and elsewhere in the world, but practical performance is still a thing for the future. I for one believe that it will be attained, and when it is attained and when it has caused the radiation dose to become so small that we can ignore it as far as somatic tissue is concerned, then at last we will be justified in employing fluoroscopy and filming as freely as we now employ such vastly less revealing procedures as inspection, palpation and auscultation.

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Some Practical Aspects of Lumbar Puncture

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Lumbar puncture in the hands of the expert is a relatively simple procedure with relatively few hazards except the insidious postspinal headache. At the same time it is a procedure in which each case deserves careful consideration and constant attention to maintain efficient technic so that patients are subjected to a minimum of discomfort while the puncture is being performed and serious complications are avoided.

SINCE lumbar puncture was first introduced in the latter part of the nineteenth century, the number of occasions on which it has been performed must rival the national income or even the national debt. One must admit that serious complications are few, but it is because the complications can be individually so distressing and sometimes crippling that constant vigilance and care are required of all those who perform lumbar puncture.

Anatomic Aspects

Although it is possible to perform lumbar puncture through an intervertebral foramen, it has generally been accepted that the easiest approach is posteriorly between the laminae of the lower lumbar vertebrae. The fact that, in the adult, the conus medullaris ends at the level of the lower border of the first lumbar vertebra or sometimes opposite the body of the second lumbar vertebra has for obvious reasons made it customary for lumbar puncture to be performed in any one of the lower three lumbar interspaces, usually between the third and fourth lumbar vertebrae. However, it should not be forgotten that in the young fetus the spinal cord fills the whole of the spinal canal, and as growth proceeds there is relative increase in length of the spinal column as compared with the spinal cord. Consequently, at birth the conus medullaris ends at approximately the inferior border of the body of the third lumbar vertebra and during early life it ascends to the final position I have described. Certain malformations, however, such as spina bifida and meningocele, may, because of fibrous adhesions, prevent the relative ascent of the spinal cord within the spinal canal.

Technic

There is controversy as to whether lumbar puncture should be performed in the midline between the spines of the lower lumbar vertebrae or slightly to one side. If the puncture is made in the midline, the needle traverses first skin and subcutaneous tissue, then the supraspinal ligament and the interspinal ligament, reaching the ligamentum flavum. Entrance of the needle into this ligament gives to the operator a sensation of resistance, and since this ligament may be as much as ½ inch (about 1.3 cm.) thick, the resistance may continue

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until there is the characteristic feeling of the needle having passed through the anterior border of this ligament, at which point the tip of the needle enters the epidural space. The operator is well advised to become conscious of the entrance of the needle into this space, which can be confirmed by the negative pressure which exists therein. When a thin rubber diaphragm is used over the hub end of the needle, as soon as the tip enters the epidural space, the rubber diaphragm is sucked in. Further advance of the needle causes it to pierce the dura mater and, since the arachnoid is, at this point, lying in intimate contact with the dura, the tip of the needle will lie within the subarachnoid space and the lumbar puncture is complete.

The lateral approach involves practically the same anatomic relations as the medial approach except that the needle does not traverse either the supraspinal ligament or the interspinal ligament, but aims at piercing the ligamentum flavum practically in the midline. The advantages claimed for this slightly lateral approach are principally that in older people it is not uncommon for the supraspinal ligament to become more than a little calcified, a condition which may deflect the needle from its intended course. Should the needle become deflected, it may proceed in a direction which would involve, superiorly, hitting against the inferior surface of the lamina above the puncture and, inferiorly, hitting against the spine or lamina below the puncture, the differentiation between these two being that the former usually occurs at a deeper level than the latter owing to the particular conformation of these bony structures. Laterally, the needle may pass through the ligamentum flavum, but in extreme cases will not pierce the dura; instead it is likely to impale one of the roots of the segmental nerve. Should the latter deflection not be too extreme, the needle will pass into the subarachnoid space but may strike one of the nerves of the cauda equina as it emerges from the dural sac and is therefore relatively fixed.

Should the needle be introduced too deeply it will strike the posterior longitudinal ligament, which lies immediately behind the disk and which is at this point relatively thin. If the needle is further advanced it may enter the annulus fibrosus of the disk or strike the body of the vertebra.

If the tip of the needle lies in the midline within the subarachnoid space, a free flow of cerebrospinal fluid will occur providing there is no obstruction of the fluid higher up in the subarachnoid space. However, if the needle lies laterally, it is possible that the flow of the cerebrospinal fluid will be obstructed by one of the nerves of the cauda equina lying against the bevel of the needle. Again, if the bevel of the needle is not entirely within the dura, it is possible that only a slow drip of the cerebrospinal fluid will result.

The fibers of the dura are largely vertical and, if the bevel of the needle passing through the dura be pointing either cephalad or caudad, the cutting edge of the needle is likely to cut the fibers of the dura. On the other hand, if the bevel lies in a lateral direction, the fibers will be split and transected. The significance of this will be discussed later in this paper.

Several investigators have described the existence of the sinovertebral nerves, which arise distal to the posterior ganglion and pass back through the intervertebral foramen, dividing within the spinal canal into several branches, some of which end in the ligamentum flavum. The cerebrospinal fluid is a clear, colorless fluid with a normal pressure of 70 to 170 mm. of water when the patient is in the lateral horizontal position.

Hazards

Hazards which may occur from lumbar puncture may be considered under three headings: (1) those occurring purely as a result of mechanical trauma arising from the insertion of the lumbar puncture needle; (2) those arising from infection, and (3) the actual complications of having introduced a needle within the subarachnoid space. The most obvious, although certainly infrequent, mechanical hazard is a broken needle. A sudden movement of the patient due to the needle's striking a nerve may be the cause of

this accident. Surgical measures are required immediately to remove the foreign body.

Trauma to the posterior longitudinal ligament and to the annulus fibrosus of the disk is said to have precipitated prolapse of the nucleus pulposus in certain cases. When one considers the average size of the spinal puncture needle, it would seem highly improbable that herniation could occur from one puncture of the annulus fibrosus. However, on this point Carnegie Dickson, in discussing the cerebrospinal fluid in meningitis, adds as an afternote that on one occasion he was puzzled by certain unusual cells in a specimen of cerebrospinal fluid. He recognized them as myelocytes due to overenthusiastic penetration of one of the vertebral bodies. To confirm this possibility, he passed a lumbar puncture needle in a cadaver through the fourth lumbar interspace into the intervertebral disk and, using a syringe under negative pressure, he was able to find several little groups of cartilage cells in the specimen so obtained.

It is not infrequent in performing lumbar puncture to obtain a so-called bloody tap. This must result from the needle penetrating blood vessels within the subarachnoid space or, more likely, the needle has advanced too far and has entered a vessel of the epidural network which is most developed anteriorly. Hemorrhage from such a puncture usually causes no aftereffects, but it is possible to suppose that hemorrhage from the extradural or epidural vessels could cause a temporary occlusion of the subarachnoid space. Cases of subarachnoid hematoma have undoubtedly occurred. The symptoms consist of headache, stiff neck, pyrexia, back pain and pain in the legs with disturbance of motor and sensory function in the lower limbs. If the hematoma can be evacuated rapidly by further puncture there may be no untoward complications, but permanent damage or fatality may result. Such a case was reported to me by Dr. Adson. The patient was a man aged 20 years on whom lumbar puncture had been performed three days previously for suspected syphilis. Laminectomy was carried out because of the diagnosis of a spinal lesion at the fourth lumbar segment. When the dura was exposed, it was shown to be bulging under marked tension and was dark in appearance, resembling the peritoneum in a case of ectopic pregnancy. The hematoma was removed with difficulty, but unfortunately the patient died that day.

Few persons who repeatedly perform lumbar puncture have not on occasions caused paresthesia despite faultless technic. These paresthesias are undoubtedly due to the needle striking a nerve of the cauda equina and the pain radiating according to the distribution of the nerve. In the hands of the less expert operator, paresthesias have been caused by the needle actually striking the root of the segmental nerve outside the subarachnoid space. Such trauma very seldom leads to any further trouble, but pains similar to the paresthesia may infrequently last for many months. Repeated puncture of the ligamentum flavum involving the sinovertebral nerve is also said to have caused chronic backache lasting for some time. Considering the number of lumbar punctures performed, disability resulting from trauma to nerves is a rare complication.

Hazards due to infection are largely preventable. Strict attention to asepsis in the preparation of the instruments used and the employment, for the performance of the procedure, of a rigid surgical technic—the operator wearing rubber gloves and mask—are a *sine qua non*. If the instruments have not been sterilized in an autoclave, they should invariably be rinsed with isotonic saline solution before use. The nature of the ampule containing the local anesthetic used for raising the skin wheal and infiltrating the supraspinal and interspinal ligaments should invariably be checked.

A lumbar puncture should never be performed through a septic area, and the skin through which the puncture is to be made should be carefully prepared. In this respect the use of an introducer is of value. It has three advantages: It prevents the spinal needle coming in contact with the skin; it diminishes the possibility of the spinal needle being deflected by calcified ligaments, and it permits the use of finer-gauge needles, which are believed to diminish the incidence of post-

spinal headache, a subject which will be discussed later. In the small, thin patient it is advisable not to insert the average introducer to its full extent because it is possible in such a patient to perform a lumbar puncture with the introducer, thus making an unnecessarily large puncture of the dura. Epidural abscess, septic spondylitis and aseptic and septic meningitis have all resulted from lumbar puncture. The two former conditions are extremely rare. Septic spondylitis has occurred as a result of performing spinal puncture in cases of septic meningitis. In considering aseptic meningitis, the literature suggests that this complication occurs as a result of spinal anesthesia rather than lumbar puncture. Septic meningitis is not necessarily the direct result of infection introduced via the spinal needle but may arise from puncture being performed on a patient already suffering from bacteremia or septicemia.

Postpuncture Headache

The hazards resulting from the actual introduction of a needle within the subarachnoid space concern principally the condition known as postpuncture headache. This condition overshadows all other complications of lumbar puncture, not because it is permanently disabling but because it is so frequent. Bier in 1889 was the first to suffer from a lumbar puncture headache, and since that time innumerable hypotheses have been submitted concerning its etiology. It is now generally accepted that the condition is due to leakage of the cerebrospinal fluid through the puncture in the dura, resulting in hypotension of the cerebrospinal fluid and disturbances in the position of the brain with tension on pain-sensitive blood vessels and sinuses. This leakage is encouraged by the negative pressure which exists in the epidural space and by the increase of cerebrospinal pressure at the site of the puncture when the patient assumes the erect position. The headache usually occurs within three days of the spinal puncture but sometimes may be delayed in onset. The puncture in the dura is said to take at least 10 days to heal. The headache usually disappears within seven days but may last much longer. It is usually frontal and bilateral in origin. It is accentuated by sitting up and relieved by the Trendelenburg supine position. Pressure on the jugular veins increases the pain. It is more common in patients less than 50 years of age than in older patients and in women than in men.

Because postpuncture headache is such a frequent complication of lumbar puncture, the temptation exists to label all headaches occurring within a few days of puncture as directly attributable to the procedure. The symptoms of postpuncture headache are classic, and it should not be confused with headaches which are unaffected by Queckenstedt's test or are less severe in the erect than in the recumbent position. Activity on the part of the patient following puncture undoubtedly predisposes to onset of this type of headache.

It is interesting to note that in a recent investigation by Marshall very low cerebrospinal fluid pressures following lumbar puncture did not *ipso facto* result in headache. He performed a second lumbar puncture on 42 patients 24 hours after the first puncture irrespective of whether the patient complained of headache or not. Five of the patients had postpuncture headaches, and in 3 of these there was hypotension of the cerebrospinal fluid. Seven of the remaining 37 were also found to have as severe a degree of hypotension, unaccompanied by any symptoms.

Prophylaxis of postpuncture headache aims at preventing leakage of cerebrospinal fluid; the smaller the puncture the less fluid escapes from the subarachnoid space after the needle is withdrawn. Hence the repeated appearance in the literature of descriptions of small-gauge atraumatic spinal needles. Multiple punctures due to faulty technic will obviously increase the sites through which cerebrospinal fluid may escape from the subarachnoid space. As I mentioned earlier, the fibers of the dura run for the most part in a cephalad-caudad direction. The bevel of the needle as it is introduced should be lying in the same plane as the fibers, which will be split and not sectioned by the cutting edge of the needle. After the puncture the patient should

remain as inactive as possible in the horizontal position.

The treatments suggested for postpuncture headache are as numerous as the hypotheses of its causation, but in general no treatment has been found to be specific in all cases. As a general rule, treatment aims at two broad principles: (1) preventing further leakage of cerebrospinal fluid, and (2) increasing the cerebrospinal fluid pressure. The former is attained by keeping the patient at complete rest in a supine Trendelenburg position in a darkened room. A variety of procedures have been suggested for increasing the cerebrospinal fluid pressure. In severe cases, injecting isotonic saline solution into the subarachnoid space has been carried out with satisfactory results, but if the leakage continues this procedure may be of only temporary value and it has the objection of creating a further exit for cerebrospinal fluid.

Increasing the osmotic pressure of the blood by the injection of hypertonic saline solution or 20 per cent solution of glucose raises the pressure of the cerebrospinal fluid. This therapy has been successful in many cases. Epidural injection of saline solution and injection of 50 cc. of macrodex within the caudal canal, a measure which Lundy has been using recently, are both aimed at preventing leakage. After the injection into the caudal canal it is advisable to have the patient sit up in bed. The intravenous injection of 100 mg. of nicotinic acid, which produces a marked vasodilatation of the cerebral vessels, has on occasions cured a postpuncture headache. Another form of treatment which also has been successful is to persuade the patient to raise his head to the limit of tolerance and thus in gradual stages assume the upright position. If the headache becomes intolerable because of too ambitious an ascent, so to speak, the patient should lie down for 30 minutes and then begin again. But the more patients one treats, the more one realizes that no single method of treatment is successful in all cases. It is, however, certain that the use of the time-tested drugs, such as aspirin and codeine, which are effective in the treatment of other forms of headache, is of little value in the treatment of postpuncture headache. Morphine may be used in severe cases.

Herniation into the Foramen Magnum

The last and most dramatic hazard which may occur as a result of hypotension of cerebrospinal fluid within the spinal portion of the subarachnoid space is the precipitation of a herniation of the medulla into the foramen magnum. This may occur in cases in which the cerebrospinal fluid pressure within the cranium is considerably increased because of cerebral abscess, subdural hematoma or tumor. Increased pressure on the respiratory center due to the herniation produces a sudden apnea which may prove fatal in a few minutes. To prevent this, as a general rule lumbar puncture should not be performed on patients who have signs of raised intracranial pressure. Should it be considered necessary to perform such a puncture, then the operator should be prepared, if the patient becomes apneic, to increase immediately the cerebrospinal fluid pressure within the spinal canal by subarachnoid injection of isotonic saline solution. At the same time a neurosurgeon should be ready for some hours following puncture to perform cerebral decompression. This condition of apnea caused by herniation through the foramen magnum is an emergency of the first order if fatalities are to be avoided. It is remarkable to watch the respiration of such a patient immediately after early decompression is performed; the improvement is most satisfactory.

Medical Examination of Prostitutes

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This article deals with the history and present status of medical examination and certification of prostitutes as measures for the protection of the public health; it states the reasons for abandonment of this practice, and for its condemnation by the American Medical Association.

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Old practices, even though long since proved unsound, die as slowly in the medical profession as in other learned professions. To cite an example, in my own field of medicine one may refer to mercury which was used for four centuries in the treatment of syphilis and which is still used by some physicians even though bismuth was proved 25 years ago to be superior; another example is the persistence in many parts of the world of the use of "rest periods" in the treatment of early syphilis. There are physicians who still depend on arsenic and bismuth for the treatment of early syphilis even though penicillin is available and has been proved far safer for the patient, easier to administer and at least as efficacious as the older therapeutic substances.

One of the slowest practices to disappear was the medical examination and certification of prostitutes as a measure for preventing the spread of venereal diseases. There are parts of the world where this procedure still has the sanction of public health authorities even though it was proved to be medically futile and socially objectionable early in the modern era of scientific diagnosis, treatment and control of syphilis, gonorrhea and other so-called venereal diseases. In the United States, Great Britain, the Scandinavian countries, Holland and Switzerland this practice has long since been abandoned by health authorities and frowned upon by the medical profession; but even in the United States there is still a handful of physicians who are willing, for a fee, to examine prostitutes and give them something to be used to encourage trade, by implying freedom from any venereal disease.

Almost from the beginning of written history it was recognized that prostitutes were an important source of the spread of infectious diseases. Moses had something to say about a condition which doubtless was gonorrhea. Within a few years after the recognition of syphilis in Europe, physicians were warning against "lying with pustulous women." In 1497 the authorities of Aberdeen, Scotland, ordered that "for protection from the disease which had come out of France and strange parts, all light women desist from their vice and sin of venery and work for their support, on pain, else, of being branded with a hot iron on their cheek and banished from the town." The vulgar name for gonorrhea

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came from the fact that the disease was so frequently acquired in the Clapier section of Paris which was the ancient restricted prostitution district.

Until about the middle of the nineteenth century, prostitution in Europe was legalized. An effort was made to segregate prostitutes in certain districts of great cities. Each woman was permanently registered with the police, from which fact came the saying "once a prostitute always a prostitute." All registered prostitutes were medically examined periodically and those thought to be infected were required to receive treatment. Many restrictions were placed on them by the police who administered the system. Prostitutes could not leave the district without permission and could leave their brothels only at certain hours. In effect, the government licensed prostitutes to carry on, under restrictions, the business of selling sexual intercourse. By collecting fees from the prostitutes, the government profited by their activity and by examining them medically the government assumed responsibility for their medical safety, just as today the government is responsible for the safety of the pork or beef it inspects. Government was a partner in the prostitution business.

This system began to come under attack on social grounds throughout the western world about the middle of the nineteenth century as a part of the great movement for human rights, social justice and the emancipation of women. With the beginning of social and governmental research, it was soon discovered that the women in the segregated districts were virtually slaves working for the profit of the madames, the owners and the agents who conducted the business. The restricted district was a market place where there was always a demand at fancy prices for young, healthy women. There was consequently an active trade, for which procurers were well paid, in seducing women and girls, luring them into brothels and detaining them there by physical or psychologic pressures. Public opinion was such that, once a girl was "broken in" and registered, there was only rarely any means of escape. To this business the term "white slave traffic" was applied.

Leading women resented the fact that prostitutes but not their male customers were subject to special laws—the so-called "double standard of morals." Later it was discovered in worldwide studies by the League of Nations that nowhere did the system accomplish what was intended. There were always more prostitutes operating outside restricted districts than inside. These independent women paid the police for the privilege of freedom from restrictions and medical inspections, thus corrupting the police and often higher officials of government.

New Concepts of Control

The regulation system was already tottering from the onslaught of social reform when the modern era of medical knowledge of venereal diseases began. With the discovery of the causal organisms of syphilis, gonorrhea, chancroid and granuloma inguinale and with the development of dark field technic and serologic tests for syphilis, it was soon evident that these diseases were far more prevalent and more damaging than previously had been suspected and that the diseases were more prevalent among prostitutes than any other group except criminals—and this in spite of all attempts at medical controls.

By 1915 it had become clear that the only scientific way and the only socially acceptable way to deal with commercialized prostitution was to divorce government from all sponsorship or responsibility for it, and to take police and social actions to reduce prostitution activities to a minimum. This was the policy adopted by the United States government at the beginning of the first world war. In place of the old system of segregation, registration and medical inspection which placed government in partnership with the prostitution business, the federal and state governments instituted programs of repression of all commercialized prostitution activities, modern measures for venereal disease control based on finding and treating all cases, education of the public, and amelioration of social conditions which lead to sex delinquency or encourage prostitution. The American Medical Association was on record in support of this program during the first world war.

Soon after 1918 laws were enacted by all states recognizing syphilis and gonorrhea as reportable communicable diseases, requiring their treat-

ment when in the infectious stages and giving the health authorities power to control these as other communicable diseases. Other laws made the practice of prostitution an offense and provided for the punishment of those who exploit and profit by prostitution activities. Even before this time the Congress and the President outlawed interstate traffic in women and girls for purposes of prostitution or lewdness—under the Mann Act.

The old red light districts disappeared, prostitution activities decreased, official medical inspection of prostitutes was discontinued, public health measures were instituted and concomitantly the incidence of venereal diseases decreased. The military incidence rates of syphilis and gonorrhea during the first world war were the lowest on record.

Between the two world wars and during and since World War II further progress has been made so that now no American city tolerates the flagrant vice conditions which were common before 1915 in areas which are now legendary—the Barbary Coast, the Levee, the Stockade, the Bull Pen, the Bucket of Blood, Skid Road and the Tenderloin. Few of my young colleagues have ever heard of these once-famous vice districts.

A few small cities still allow brothels to operate in acknowledged violation of state laws and city ordinances. In some of these cities a few physicians, because of ignorance or greed, were found in recent studies made by the American Social Hygiene Association to be examining prostitutes and giving them documents which could be used in soliciting business. With the public better informed about the dangers of venereal diseases, prostitutes and their agents urgently desire to have means of deluding prospective customers into believing the risks of infection are nil. A name with an M.D. after it, whether on a card carried by the prostitute or posted in her room, serves this purpose even if it only states that a blood test was negative.

The American Social Hygiene Association's studies in 200 communities in 1950 and 1951 discovered 20 physicians in 14 towns and small cities in 10 states to be routinely examining prostitutes and giving them some type of document to show that a medical examination had been made. The usual practice of these doctors was to examine prostitutes every two weeks; a smear was taken for microscopic examination and once a month specimens were taken for serologic tests. The fee charged usually ranged from $3 to $5 per person per examination. The prostitute herself paid the fee. If a prostitute were found to be infected, she might be treated by the examining physician or, if she were penniless, she might be referred to a clinic.

"Tests" Are Unreliable

The smears taken by these physicians may be stained and examined by the doctor himself or sent to the health department. In either case, even assuming that the specimens are taken skillfully, the microscopic examinations of secretions from the female genitalia are notoriously unreliable. Even when specimens are expertly taken, the Gram stain is employed and the microscopic study is done by a skillful person, 15 per cent of cases of gonorrhea are missed as compared with the findings where culture methods are employed.

Prostitutes, their agents and the physicians who examine and certify them attach great weight to a "negative" blood test. This is because both the prostitute and her customer believe a negative blood test definitely means freedom not only from syphilis but also from any "VD." Of course the fact is that a negative serologic test does not indicate freedom from syphilis, nor does a positive test indicate syphilis in a communicable stage—nor even necessarily syphilis *in any stage* if unsupported by additional serology or history and clinical findings. In the hands of a madame, prostitute or panderer, however, a report of a "negative blood test" is a valuable asset, increasing the salability of the services of these women.

One frequently hears the question, "Why doesn't the Health Department examine prostitutes, weed out the infected and allow the others to carry on—as they do in Europe?" The fact is that in a large part of Europe this practice has long since been abandoned for the same reasons it has been abandoned in the United States. Only in a few backward areas or

where the prostitution business is politically so deeply entrenched as to defy medical and social opinion is medical inspection continued today. Before the recent war I studied medical inspections of prostitutes in nearly every country of Europe where they were legalized. The examining doctors devoted less than five minutes to inspecting and taking specimens from each prostitute. Specimens were taken in a perfunctory manner. The Gram stain was rarely employed and cultures never done. Only occasionally was the dark field microscope used. A few grossly infected cases were discovered, and these women were sent for treatment, returned to the ranks of prostitutes, reinfected and sent again and again for treatment—a veritable venereal merry-go-round. The physicians who made these examinations confidentially asserted their belief that the whole process was futile; "but," they added, "the pay is good, and one must live."

It should be pointed out that our knowledge of the epidemiology of the five common venereal diseases—syphilis, gonorrhea, chancroid, granuloma inguinale and lymphogranuloma venereum—is very new and still imperfect. With regard to one of these diseases, granuloma inguinale, it is even doubtful whether it is a communicable disease in the ordinary sense. The more one learns about syphilis, the less dogmatic is one inclined to be about the limitations of its resourcefulness in passing from one human being to another.

Difficulties of Examination

Consider the anatomy of the female genitalia and the structures which can be subjected to examination in a physician's office by inspection and by taking specimens for laboratory procedures. The whole genitoanal region must be inspected and any suspicious lesion examined. A brief description could be as follows:

The vagina is a pocket three to four inches deep with highly expansile, corrugated walls containing numerous lymph glands. It is closed at one end by the neck of the uterus, which contains many glands and is penetrated by a small canal, lined by other thousands of glands, leading from the vagina into the cavity of the uterus. The pocket is open at the other end but the entrance is surrounded by folds of tissue, the labia containing still more glands. In close proximity supero-anteriorly is the opening of the urethra, surrounded by glands. These glands discharge secretions onto the surfaces of the cervix, the walls of the vagina, the labia minora and majora and the orifice of the urethra. All these glands are particularly susceptible to gonococcus infection. Posteriorly is the anus. The early lesions of syphilis, chancroid, granuloma inguinale and lymphogranuloma venereum may be found anywhere in this area. Indeed, about 6 per cent of chancres are completely extragenital, the lip being the commonest extragenital site of lesions.

The skillful and conscientious examiner approaches these structures with a vaginal speculum, a good light and equipment for taking specimens of secretions and tissues. He knows that any gland may be the site of gonococcal infection whether it opens onto a visible surface or into the canal of the cervix. He knows that any lesion he can see may contain *Spirochaeta pallida* but also that an infectious lesion may be too small to be detected or may be hidden behind the rugas of the vagina. He may know that the spirochete of syphilis has been recovered by abrading the wall of the vagina even when no lesion has been found, and that the gonococcus and Ducrey's bacillus have been cultured from discharges within the female genital tract even when there was no visible evidence of disease.

Specimens from any lesion that the examiner can find must be examined for evidence of syphilis by the dark field method, for Donovan bodies of granuloma inguinale by biopsy and Wright's stain, and for *Hemophilus ducreyi* by the Gram stain and by cultures. A search for the gonococcus will not have been adequate until specimens have been properly taken from the cervix—including the orifice of the cervical canal, Bartholin's glands and the urethra—stained by the Gram method and put through the culture procedure including the fermentation test. If there is any suggestion or possibility of chancroid or lymphogranuloma venereum, the appropriate intradermal tests (Ito-Reenstierna and Frei) must be performed. Blood must be taken for serologic tests for syphilis.

Having completed such an examination, taken the appropriate specimens and made the appropriate skin tests, the physician must wait at least three or four days for the results of his laboratory and other tests. When all tests are negative, he must repeat the procedure if any lesion was found which could be syphilis, granuloma inguinale, chancroid or lymphogranuloma venereum—and in a prostitute any genital lesion may be evidence of any one or even all of these diseases. In such subjects one negative examination means precisely nothing.

If the female subject of such an examination is a promiscuous person—for example, a prostitute—she may become infected within an hour after she leaves the physician's examining room by the next person having intercourse with her. It is hardly practicable to examine prostitutes after each sexual contact, especially as many have relations with more than 20 men per day. The cost of an adequate examination—estimated at $35 to $50—and the time required—30 to 60 minutes each—render even daily examinations impracticable. Even if such examinations were possible and practicable, no conscientious physician would certify a prostitute as free from any venereal disease at any given time because he would admit to himself that no matter how skillful and experienced he may be he could easily have missed a lesion or failed to express infective material from a gland, or a laboratory procedure may have failed.

Regulations Against Examination and Certification

Every one of the 48 states of the United States and every Territory has laws against prostitution or aiding and abetting prostitution. These laws are not only for the protection of the public health but also for the safeguarding of public morals and decency. With relatively few notable exceptions the state laws and city ordinances against commercialized prostitution are now well enforced in the United States.

Certain states have laws prohibiting the examination and certification of prostitutes. A typical provision reads as follows:

> No physician shall issue a certificate to any person stating such person is free from any venereal disease except after careful clinical and laboratory examination, and unless such physician shall first have satisfied himself or herself that such certificate is not intended to be used for solicitation for sexual intercourse.

Medical examination of prostitutes as a measure for the protection of the public health is not only futile but also misleading. It does not rest on a sound scientific or a sound social basis. It is for these reasons that the American Medical Association has on two occasions—in 1942 and again in 1945—made the following declaration:

> First, that the control of venereal disease requires elimination of commercialized prostitution; second, that medical inspection of prostitutes is untrustworthy, inefficient, gives a false sense of security and fails to prevent the spread of infection; third, that commercialized prostitution is unlawful, and physicians who knowingly examine prostitutes for the purpose of providing them with medical certificates to be used in soliciting are participating in an illegal activity and are violating the principles of accepted professional ethics.

The *Journal of the American Medical Association* for June 9, 1951, in an editorial on this subject, declared: "Patriotic motives, as well as a decent respect for medical ethics and law, should lead those few physicians who have been cooperating with prostitution rackets immediately to cease examining and certifying the unfortunate women who are exploited in a vicious traffic."

Physicians have played a leading role in bringing about the progress against venereal diseases and against prostitution—an advance in public health, social welfare and good government which is in part responsible for the substantial decrease recently noticed in the incidence of syphilis. The action taken by the House of Delegates of the American Medical Association on this subject and the editorial in the *Journal of the American Medical Association* have further contributed to progress by informing or warning the few physicians who examine and certify prostitutes that this practice is unsound medically, unethical in the view of organized medicine, and in some states illegal. It is reasonable to hope that future studies will find fewer and fewer physicians willing to cooperate with prostitutes, pimps and corrupt officials in an illegal racket.

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Current Use of Antibiotics

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INDICATIONS for and methods of the use of various antibiotics are changing so rapidly that a review of this subject seems justifiable. By definition, an antibiotic is a substance of biologic or microbial origin that possesses antibacterial activity.

Antibiotic agents of microbial origin are derived from three general sources: (1) They may come from bacteria. This group includes pyocyanase, which is the earliest known antibiotic, and tyrothricin. (2) They may be derived from molds and fungi. The most important of this group is penicillin. (3) They may come from the *Actinomyces*. The most promising of this group at the moment appear to be streptomycin, chloramphenicol, AUREOMYCIN® and terramycin.

The antibiotic agents that are in current clinical use are listed in Table 1. Penicillin, streptomycin, chloramphenicol, aureomycin and terramycin possess rather selective antibacterial activity and at the same time are sufficiently nontoxic to permit either oral or parenteral administration for considerable periods. Many of the other antibiotic agents that inhibit pathogenic bacteria can be used only for local treatment because of the toxic effects that follow systemic administration.

Since textbooks are available that deal with the antibacterial activity and pharmacology of these substances, I shall not attempt a review of these subjects. Rather, this discussion will concern itself with dosage, method of administration, clinical use and toxicity.

Dosage and Method of Administration

Penicillin—When penicillin first became available, most investigators used relatively small amounts in order to spread a limited supply as far as possible. As supplies increased, the recommended daily dose also increased, apparently with the idea that if a little was good, more was better. Although opinions differ greatly as to the proper dose of penicillin, a total daily dose of 300,000 to

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TABLE 1

ANTIBIOTIC AGENTS IN CURRENT USE

ANTIBIOTIC AGENT	SOURCE	FIRST REPORTED BY	METHOD OF ADMINISTRATION	SUSCEPTIBLE ORGANISMS
Bacitracin	*Bacillus subtilis*	Johnson, Anker and Meleny (1945)	Topical	Gram-positive Some gram-negative
Tyrothricin	*B. brevis*	Dubos (1939)	Topical	Gram-positive
Gramicidin	*B. brevis*	Hotchkiss and Dubos (1940)	Topical	Gram-positive
Polymyxin A	*B. polymyxa*	Stansly, Shepherd and White* (1947)	Topical	Gram-negative Some gram-positive
Polymyxin B	*B. aerosporus*	Ainsworth, Brown and Brownlee (1947)	Topical	Gram-negative Some gram-positive
Penicillin	*Penicillium notatum*	Fleming (1929)	Systemic Topical	Gram-positive Some gram-negative
Streptomycin	*Streptomyces griseus*	Schatz, Bugie and Waksman (1944)	Systemic Topical	Gram-negative Gram-positive
Chloramphenicol	*Str. venezuelae*	Ehrlich, Bartz, Smith, Joslyn and Burkholder (1947)	Systemic Topical	Gram-positive Gram-negative *Rickettsia*
Aureomycin	*S. aureofaciens*	Duggar (1948)	Systemic Topical	Gram-positive Gram-negative *Rickettsia*
Terramycin	*S. rimosus*	Finlay and colleagues (1950)	Systemic Topical	Gram-positive Gram-negative *Rickettsia*
Neomycin	*S. fradeae*	Waksman (1949)	Topical	*Mycobacterium tuberculosis* Gram-negative and gram-positive
Viomycin	*S. floridae or puniceus*	Finlay and colleagues† (1950)	Topical	*Myco. tuberculosis*

*Simultaneously, polymyxin A was under investigation by Benedict and Langlykke.
†Simultaneously, viomycin was under investigation by Ehrlich, Smith, Penner, Anderson and Bratton.

400,000 units is usually enough to accomplish a cure of those infections caused by organisms that are susceptible to its action.

The two types of administration most commonly used are the method of repeated intramuscular injections and the method of continuous intravenous drip. In the intermittent intramuscular method the usual recommended dose for adults is 40,000 units of aqueous suspension of penicillin every three hours. For children and infants the usual recommended dose is 10,000 to 20,000 units every three hours.

The discovery that certain substances, when added to penicillin, greatly prolonged its action was an important advance in therapy with penicillin. The preparation most commonly used at present consists of 300,000 units of procaine penicillin G per cubic centimeter of aqueous suspension.

A preparation is now available which contains 600,000 units of crystalline procaine penicillin G per cubic centimeter of aqueous suspension. Many physicians apparently are of the opinion that the preparation containing 600,000 units per dose is twice as good

as that containing 300,000 units. It is true that use of the 600,000 unit preparation maintains a therapeutic quantity of antibiotic in the blood for longer periods, but the maximal value in the blood is lower than when the 300,000 unit preparation is used. Therefore, in most instances it would seem advisable to administer 300,000 units at a time and at more frequent intervals.

In my opinion, the method of intravenous drip is the best form of treatment for overwhelming infections, such as bacteremia or subacute bacterial endocarditis. The administration of penicillin by this method should be used for at least the first few days of treatment of these infections. At least 1,000,000 units of penicillin in 2000 cc. of physiologic saline solution should be given daily. If the rate of flow is adjusted to 20 to 25 drops per minute the infusion will, as a rule, take 24 hours.

Solutions containing various amounts of penicillin dissolved in physiologic saline solution can be injected directly into body cavities. There has arisen considerable controversy on the addition of penicillin to the cerebrospinal fluid. Some clinicians believe that penicillin so administered produces adhesive arachnoiditis. It is my opinion that if the daily dose does not exceed 10,000 units this complication will not occur.

Penicillin may be administered orally. Its oral use in the treatment of severe, life-endangering infections is to be condemned, however. Individual variations in the absorption of penicillin after its oral administration are great and, at present, the expense of oral use is greater than with the intramuscular method of treatment.

Penicillin may be administered by nebulization through a standard glass nebulizer operated by compressed air. Although the powder inhalators are more convenient, the therapeutic efficacy of penicillin in the form of these relatively large particles is less than when solutions of penicillin are nebulized with compressed air. Therefore, powder inhalators should not be used in the treatment of serious types of pulmonary infection.

The concentration of penicillin in the blood may be increased by the simultaneous administration of substances which block the excretion of penicillin by the kidneys. Carinamide, first used for this purpose, has been discarded in favor of p-(di-n-propylsulfamyl)-benzoic acid (benemid). The recommended dose of benemid for adults consists of 0.5 gm. every six hours.

Streptomycin—The original or so-called regular streptomycin has been replaced almost universally by dihydrostreptomycin. The chief interest in dihydrostreptomycin obviously centers about the fact that this hydrogenated material appears to be considerably less toxic than regular streptomycin. Hereafter in this paper, what is written concerning streptomycin is to be interpreted as referring to dihydrostreptomycin.

Streptomycin is usually administered by the intramuscular route. When treatment is to be continued no longer than 12 to 14 days the recommended dose is 2 gm. daily. One gram is administered intramuscularly every 12 hours. If treatment is to be continued beyond this period it is recommended that the daily dose be 1 gm.

When streptomycin is given intrathecally, as is recommended in the treatment of coccal, bacillary and tuberculous meningitis, the recommended dose for adults is 50 to 100 mg. in 10 cc. of physiologic saline solution. This amount should be administered every 48 hours until cultures of cerebrospinal fluid become sterile. For young children and infants the recommended dose of streptomycin for intrathecal use is 25 to 50 mg. in 5 cc. of physiologic saline solution.

Streptomycin may be used for nebulization in a manner similar to that described for penicillin.

Chloramphenicol—This substance usually is given orally. The dosage varies with the disease being treated. In general, the initial dose for an adult is calculated on the basis of administration of 50 to 75 mg. per kilogram of body weight, and this is followed by a dose of 0.25 to 0.5 gm. every three to four hours thereafter.

Aureomycin—This antibiotic agent, as is true with chloramphenicol, is usually admin-

istered orally. The recommended oral dose of aureomycin in the treatment of infections owing to organisms susceptible to its action is as follows: 750 mg. should be administered every six hours for adults; for children, 500 mg. should be given every six hours; for younger children and infants, 250 mg. should be given every six hours.

When gastrointestinal irritation is produced by aureomycin, it usually can be controlled by simultaneous administration of a glass of cold milk or 15 gr. (1 gm.) of sodium bicarbonate. If these measures fail, aureomycin calcium caseinate often can be substituted with excellent results.

A satisfactory method for administration of aureomycin to patients in whom intranasal catheters for suction are being used is simply to put the contents of the capsule into a feeding formula and administer the mixture through the catheter. If the catheter is then clamped for approximately two hours, absorption of the aureomycin will occur.

If, for any reason, patients are unable to receive aureomycin by the oral route, it may be desirable to administer it intravenously. The recommended dose of aureomycin for intravenous use for adults is 500 mg. every 12 hours. This amount is dissolved in 250 to 300 cc. of physiologic saline solution and is administered at a fairly rapid rate through an 18 gauge intravenous needle. Aureomycin should not be injected into the veins of the lower extremities. Repeated injections of aureomycin produce venous irritation and thrombosis that, in turn, may result in embolic phenomena. Therefore, intravenous injections of aureomycin should always be given in the upper extremities, since embolic phenomena from the upper extremities are extremely rare. Considerable degrees of local irritation and pain result from the intramuscular injection of aureomycin, and in its present form this antibiotic should not be given by this route. Solutions of aureomycin should not be instilled into body cavities, such as the pleura, peritoneum, cerebrospinal canal or joint spaces.

Terramycin—The dose and the method of administration of terramycin are practically identical to those of aureomycin. Neither aureomycin nor terramycin is absorbed after rectal administration.

Prophylactic Uses of the Antibiotics

The prophylactic use of these substances should be considered before their clinical use is discussed. Since penicillin, aureomycin and terramycin possess the widest range of antibacterial activity, these three antibiotics are most suitable for prophylactic treatment. Serious diseases such as rheumatic fever often can be prevented by simple prophylactic use of these preparations. However, because of the expense of antibiotics the sulfonamide compounds still enjoy widespread use in the prevention of rheumatic fever.

Another important prophylactic use of these agents concerns the prevention of subacute bacterial endocarditis. Although great advances have been made in the treatment of this disease, therapy often is long and costly and sometimes unsuccessful. It is my opinion that antibiotics should be employed prophylactically when patients who have cardiac murmurs undergo surgical procedures of certain types. The general term "cardiac murmurs" is used because it is often difficult or impossible to differentiate organic and functional murmurs. The risk of subacute bacterial endocarditis is sufficient to justify use of prophylaxis unless the physician is certain that the murmur is functional. The operations that are most frequently followed by subacute bacterial endocarditis involve the mouth, nose, throat, intestine, rectum or prostate. Surgical procedures that directly involve the heart present another important indication for prophylaxis of this type.

In general, satisfactory prophylaxis usually can be accomplished by antibiotic therapy for one or two days before operation and for a few days during the postoperative period. Procaine penicillin is the preparation of choice because it is well suited for this purpose and is relatively inexpensive. The prophylactic use of antibiotics is indicated also whenever gross and obvious contamination of the peritoneal cavity has occurred.

Clinical Uses of Penicillin and Streptomycin

Complete discussion of the clinical use of these substances is not practical in this presentation. Two diseases, however, seem worthy of special mention. These are acute mastoiditis and cavernous sinus thrombosis, which occur usually as serious complications of otherwise benign infections. A few years ago these two conditions were encountered rather frequently and their outcome was often fatal. Since the advent of penicillin and its widespread use in the early treatment of the underlying infections, acute mastoiditis and cavernous sinus thrombosis have been reduced to a place of minor importance. The use of penicillin and streptomycin has produced significant changes in the morbidity and mortality of many serious infectious diseases. Discussion of the most recent advances regarding these antibiotics will be included in the consideration of combined antibiotic therapy.

Clinical Uses of Aureomycin

The similarity between the antibacterial activity in vitro of penicillin and aureomycin has been established. Investigation has also substantiated the fact that the action of these antibiotics is similar clinically. However, I shall mention a few diseases that are resistant to penicillin but that do respond to the action of aureomycin.

Disease caused by penicillin-resistant Micrococcus pyogenes var. aureus—Before 1944 only a few strains of penicillin-resistant micrococci (staphylococci) were encountered. Since that time a number of investigators have reported on the increased incidence of strains of staphylococci which are resistant to penicillin. For example, in 1946 only 14 per cent of staphylococci cultured from patients in a certain hospital were resistant to penicillin. In 1948 the number had increased to 59 per cent and in 1949 to 68 per cent. The cause of this increase in the number of resistant staphylococci is still questionable. Originally most of the resistant strains were sensitive to the action of aureomycin. Unfortunately, however, in recent months an increasing number of aureomycin-resistant staphylococci have been encountered.

Primary atypical pneumonia—Considerable controversy previously existed about the effects of aureomycin in the treatment of primary atypical pneumonia. This is not surprising since it is extremely difficult to assess the value of any drug in the treatment of a disease with such a variable course as that of primary atypical pneumonia. A number of investigators now agree that aureomycin exerts a definite and beneficial effect on the course of so-called viral or atypical pneumonia. However, the published data contain little to support the value of aureomycin in certain other important viral infections, such as the common cold, influenza, poliomyelitis, encephalitis, variola and rubeola.

Rickettsial diseases—Many reports are now available concerning the use of aureomycin in the treatment of rickettsial diseases. These diseases include Q fever, typhus, scrub typhus, Rocky Mountain spotted fever and rickettsialpox. On the basis of extensive clinical studies, aureomycin appears to be an extremely effective agent in treating rickettsial diseases.

Miscellaneous disorders—The successful use of aureomycin in the treatment of amebiasis has been reported by many investigators. Aureomycin is the most effective agent available at present for the removal of bacteria from the intestinal tract. Most bacteria, with the exception of *Proteus* and *Pseudomonas*, are removed from the intestinal contents after administration of aureomycin. This is an important contribution to the preoperative preparation of patients for surgical procedures involving the intestinal tract. The recommended oral dose of aureomycin is 750 mg. four times daily for three or three and a half days prior to operation.

The use of antibiotics in the therapy of pertussis has received considerable attention. Many clinical investigators were of the opinion that streptomycin was of value in the treatment of this disease. More recently, use of aureomycin has been suggested as the treatment of choice. Further clinical investigation is necessary before it can be settled.

Clinical Uses of Terramycin

Numerous laboratory and clinical reports indicate that aureomycin and terramycin have similar actions both in vivo and in vitro. There are, however, some differences. For example, terramycin appears to be more effective in the treatment of certain rickettsial diseases. Since the clinical use of these two drugs is so similar, the reader is referred to the preceding discussion concerning aureomycin.

Clinical Uses of Chloramphenicol

Typhoid fever—Early investigation suggested that chloramphenicol exerted a specific therapeutic effect on the course of typhoid fever. In this regard it is unique among present antibiotics. Although chloramphenicol resembles aureomycin and terramycin in some respects, it is far superior in the treatment of typhoid fever. However, serious toxic reactions may follow its administration. Nevertheless, it is my opinion that at present chloramphenicol is the antibiotic of choice in the treatment of typhoid fever.

Combined Antibiotic Therapy

Combined therapy represents probably the most significant recent advance in treatment with antibiotics. Before 1947 a combination of penicillin and dihydrostreptomycin was used more or less empirically. Since 1947 a number of studies have been reported that demonstrate a synergistic effect between these two drugs. However, certain antibiotics in combination are antagonistic and thus their union is contraindicated. Penicillin has been found to be more effective when used alone than in combination with aureomycin or chloramphenicol. Since aureomycin and terramycin are so similar it would seem safe to include terramycin in this group. Theoretically, then, penicillin should not be used in combination with aureomycin, chloramphenicol or terramycin.

At present the data concerning the use of combined therapy are still somewhat limited. However, there are a few diseases in which combined therapy seems justified.

Brucellosis—Several drugs or combinations of drugs have been used previously in the treatment of this disease. That therapy of this type was unsuccessful is evident from the significant rate of relapse. At present it is my opinion that the treatment of choice for brucellosis consists of a combination of either aureomycin or terramycin with dihydrostreptomycin. In one series more than 50 patients have been observed who were treated by this method for systemic or bacteremic brucellosis. Only one bacteriologic relapse occurred in this group, and some of these patients have been studied for as long as two years. Patients with systemic or bacteremic brucellosis are given 3 gm. of aureomycin or terramycin and 2 gm. of dihydrostreptomycin daily for 12 to 14 days. On the other hand, if localized lesions are present, including those of the urinary tract, skeletal system or lymph nodes, the recommended dose is 3 gm. of aureomycin or terramycin combined with 1 gm. of dihydrostreptomycin daily for 28 days.

Subacute bacterial endocarditis—Combined therapy has also been found to be of value in the treatment of this disease. Patients with endocarditis caused by the various groups of streptococci usually respond well to treatment with penicillin alone. However, in about 3 to 10 per cent of these patients the infection is caused by highly resistant organisms. These resistant organisms are classed as enterococci, of which *Streptococcus faecalis* is one of the commonest. At present the treatment of choice in enterococcal subacute bacterial endocarditis is a combination of penicillin and dihydrostreptomycin. The optimal dose of these two substances remains to be determined. When subacute bacterial endocarditis is produced by an unknown organism, a combination of these two drugs should be used. Investigation is also under way at present concerning the use of combinations of penicillin and dihydrostreptomycin in the treatment of all types of subacute bacterial endocarditis, regardless of the sensitivity of the organism. It is hoped that this type of therapy may substantially reduce the length of treatment. At present the results of the use of aureomycin and terramy-

cin in the treatment of subacute bacterial endocarditis have been disappointing.

Bacteremia, peritonitis and meningitis—When the organisms causing these infections are known, the antibiotic of choice usually can be determined with little difficulty. However, if the organisms producing these infections are unknown, the recommended treatment consists of a combination of either aureomycin or terramycin with dihydrostreptomycin. Use of aureomycin or terramycin is preferable to use of penicillin since the former have a wider antibacterial spectrum. In the treatment of meningitis it is well to remember that terramycin does not diffuse into the cerebrospinal fluid. The suggested dose is 3 gm. of aureomycin or terramycin daily combined with 2 gm. of dihydrostreptomycin. If treatment is to be continued for more than two weeks, the daily dose of dihydrostreptomycin should be 1 gm. It should be emphasized that much of the work concerning combined therapy consists of laboratory studies. Further clinical trials are necessary before final statements can be made regarding optimal doses and the combinations of choice.

Toxicity of Antibiotics

Penicillin—The common toxic reactions caused by penicillin are familiar. I should like to comment only on the cutaneous reactions. Dermatitis following the use of this substance may be extremely severe. This type of dermatitis often can be controlled by the use of tripelennamine hydrochloride (PYRIBENZAMINE®) or of diphenhydramine hydrochloride (BENADRYL®). If these measures are not successful, administration of cortisone often produces spectacular results. Usually 100 mg. is administered for two to three days, after which gradually decreasing amounts are given.

Streptomycin—Streptomycin, unlike penicillin, produces well recognized neurotoxicity. When treatment with streptomycin is continued for several weeks, vertigo or ataxic gait may develop. Likewise, administration of streptomycin may cause nerve deafness. At the earliest sign of this complication, the antibiotic probably should be discontinued.

Aureomycin and terramycin—Since the toxic reactions produced by the administration of these two substances are practically the same, they will be discussed together. After administration of these substances it is not uncommon to encounter gastrointestinal irritation manifested by nausea and vomiting. As previously stated, this usually is controlled readily by the simultaneous administration of a glass of cold milk, 15 gr. (1 gm.) of sodium bicarbonate or, if necessary, the substitution of aureomycin calcium caseinate. Cutaneous reactions produced by aureomycin or terramycin do occur but are extremely rare. Other toxic reactions that occur occasionally include diarrhea, pruritus ani and pruritus vulvae. When more than the recommended dose of 0.5 gm. of aureomycin is given by the intravenous route, certain mild toxic effects may be experienced. When as much as 1 gm. of aureomycin is administered intravenously in a single injection, nausea and vomiting may occur occasionally and mild febrile reactions may be induced.

Chloramphenicol—The fact that chloramphenicol contains the nitrobenzene radical suggested that this drug might be toxic to the hemopoietic system. Several instances of aplastic anemia and death following the use of chloramphenicol have recently been reported.* The clinician will do well to remember that use of chloramphenicol may be followed by disastrous results.

*Claudon, D. B. and Holbrook, A. A.: Fatal aplastic anemia associated with chloramphenicol (CHLOROMYCETIN®) therapy; Smily, R. K., Cartwright, G. E. and Wintrobe, M. M.: Fatal aplastic anemia following chloramphenicol (CHLOROMYCETIN®) administration; Sturgeon, P.: Fatal aplastic anemia in children following chloramphenicol (CHLOROMYCETIN®) therapy. J.A.M.A. 149:10 (July 5) 1952.

SCIENTIFIC EXHIBIT

Congenital Laryngeal Stridor

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CONGENITAL laryngeal stridor is not an uncommon form of stridor, beginning at or soon after birth and continuing until around the second year of life. It is difficult to determine any predisposing factors that might have some bearing on the etiology of this condition. It has been described as a congenital malformation of the vestibule of the larynx. The stridor which is the characteristic symptom is noticed at or soon after birth. In some cases it may not be apparent until several weeks after birth although it is likely that there was some difficulty in breathing which went unnoticed during the early days of life.

The stridor is usually the reason for parents seeking medical advice. The character of the sound varies. It may be similar to grunting, the purring of a cat or the croaking of a frog. The inspiratory stridor is always louder than the expiratory phase. The stridor tends to diminish when the child is asleep or being nursed; it is likely to increase when the child is awakened or stimulated. There is no hoarseness in the cry or cough. There is usually retraction of the thorax and abdomen. There may be some change in the form of the chest, the most common being a depression of the inferior portion of the sternum. In spite of this evidence of obstructive breathing, cyanosis is almost never seen.

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ADAPTED FROM AN EXHIBIT SHOWN AT THE ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION (ATLANTIC CITY).

This illustrates extreme respiratory distress.

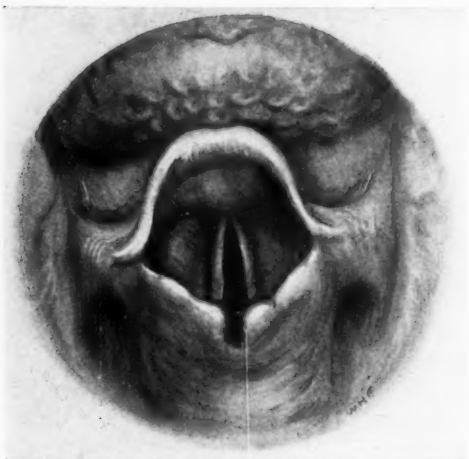
The epiglottis is pulled down over the glottic chink with inspiration.

The examination of the larynx is done by direct laryngoscopy and until this method was available, little was known about the mechanism responsible for the condition. A classic description was given by Lambert Lack: "The epiglottis was sharply folded on itself, the two lateral folds being in close apposition and in some cases in contact. The aryepiglottic folds were approximated and thus the upper aperture of the larynx was reduced to a long, narrow slit. The thin folds bounding this aperture seemed quite flaccid and flapped to and fro on respiration. The inspiratory column of air striking down on these folds drove them together and on expiration they were separated. In some cases, the purring ones, the coarse vibration of the cords could be distinctly seen."

On direct laryngoscopy, the attachment of the epiglottis may appear inadequate on one side or both so that the epiglottis is drawn to one side and down over the glottic chink on inspiration. The aryepiglottic folds bound a narrow space and the distance from the edges of the aryepiglottic folds to the level of the true cords appears greater than in a normal infant larynx. Thus, on inspiration, the stridor is pro-

The epiglottis is folded upon itself and pulled down over the glottic chink on inspiration. The attachment of the epiglottis appeared to be more flaccid on the right side.

The epiglottis is folded upon itself obstructing the airway on inspiration.



Normal appearing larynx at two years of age at which time infants with congenital laryngeal stridor usually have a normal airway.

Two year old child with normal airway.

duced by the epiglottis being drawn down over the chink and the close approximation of the aryepiglottic folds.

In the differential diagnosis, one must consider bilateral choanal atresia, congenital glottic stenosis, nonspecific laryngitis, growth in the larynx (the most common being papillomas), vascular ring and lack of cartilage in the tracheobronchial tree. Direct examination of the larynx is important in establishing the diagnosis. Congenital laryngeal stridor commences early in life and is not sudden and acute in its onset. The stridor is characteristic and is accompanied by some evidence of obstructive respiration. The cry is not hoarse and the stridor occurs throughout the day and even at night with short intervals of quiet breathing. In general, the health is good and there is no evidence of infection.

The prognosis is good; the condition tends to disappear by the second year of life or sooner.

The treatment consists of maintaining the general health of the child. Reassurance of the parents is most important. Others have reported the need of tracheotomy in an occasional case but this has not happened in our experience.

Pediatrics IN GENERAL PRACTICE

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Foot Problems in Children

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THE great majority of foot problems in children can and should be managed by the family physician. These problems present the opportunity to establish a pleasant relationship with the child and to begin teaching personal responsibility for health and medical problems. For purposes of this paper we shall omit consideration of frankly orthopedic problems, such as clubfoot, spina bifida, talipes equinus, metatarsus varus, and problems associated with poliomyelitis, cerebral palsy and other neurologic entities. Similarly, we shall assume that the child to be treated is within the normal range in reference to reflexes, motor power, equality of length and circumference of limbs and also that he has free range of his joint motions in the lower extremities.

The anatomy of the foot of the average normal infant has received lengthy consideration elsewhere. The transverse and longitudinal arches are present in soft cartilaginous and ligamentous structures, their contours concealed by adipose tissue. The feet are susceptible to moulding by external forces at an early age, as is well recognized in the treatment of congenital clubfoot. The action of muscles has a profound influence on the shape of the growing foot, the "sling" action of the anterior and posterior tibial muscles being clearly related to the contours and function of the longitudinal arch. In the absence of the normal tonus and function of these muscles, contours of the arch are lost, the ligamentous structures alone being unable to direct the growth of the bones along paths of normal development. Any musculoskeletal or neurologic imbalance which allows function of the foot or lower extremity in an abnormal attitude will lead to progressive deformity during the period of growth of the child. Factors such as chronic illness, malnutrition, vitamin deficiency and hereditary patterns all result in early and rather rapid changes in the shape and alignment of the weight-bearing limbs. Similarly, therapeutic measures which restore the limbs to a neutral position during function, eliminating the deforming tendencies, will show gratifying results coincident with growth of the child.

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History

The first step in arriving at a diagnosis of a child's foot problem and at an appropriate

plan of treatment requires a careful history. If the child is old enough to give some of the information himself it is wise to ask him for it; things which bother only the parent frequently require rather different therapy than those which bother the child. A gait which may be objectionable to the mother may be based not on a medical problem but on copying some older person or playmate. Maternal concern over suspected bowleg, knock knees or flatfoot is frequently caused by its presence in one of the child's parents. If the child is said to have pain, some quantitative measure is frequently helpful, i.e., does it limit play, cause limp, require rest or medication, interfere with sleep, require carrying the child on long walks or upstairs.

Insight into underlying factors in the child's difficulty can commonly be obtained by routine pediatric questioning as to the motor developmental history, the administration of vitamin supplements and adequacy of the early infant diet, intercurrent illnesses, the type of shoes used as "pre-walkers" and in early walking efforts, the age when weight-bearing started, and the presence of similar problems in other children in the family.

Certain lesions are related to positional factors in the infant: Does the baby always sleep on his abdomen with the toes pointing toward each other? (Many such children have internal torsion of the tibias and a "ding-toe gait.") Effect of the child's problem on his shoes should be determined. Are they run over on the sides? Are they too large? Do parents get him new shoes because the old ones are too small or worn out, or just because a certain time interval has gone by?

Examination

Examination of the child with all clothing removed is desirable. The general posture may reflect the specific complaint, revealing rounded shoulders, lordosis, abdominal ptosis, as well as genu valgum and flatfoot. The legs and feet should be examined while walking and standing, and with body weight removed. If genu valgum is complained of, a quantitative measure is useful for future reference: Note the distance separating the medial malleoli as the child stands relaxed with the inner aspects of his knees barely in contact. Observe for possible stigmas of healing or old rickets. Check the flexibility of the spinal column, the ability to touch the floor with the fingertips, possible tight hamstrings or heel cords. Note the level of the iliac crests in considering the equality of leg lengths. Observe the child's gait with shoes on as well as off, and the effect of his present shoes on the deformity. Note the height of the child's longitudinal arches as he stands relaxed, compared with contours when he flexes his toes and walks on the lateral borders of his feet. Are his "flat feet" due to poor use of his muscles (perhaps generally) or based on bony deformity? Note the relative transverse axes of the knee and ankle joints: Is his toeing-in caused by a rotation of the entire leg at the hip, by torsion through the tibia alone, or by adduction of the forefoot (metatarsus varus)? Check to see that the child's stockings are not too short, causing curling of his toes and toeing-in. Check the shoes to see whether the child's complaints are reflected in abnormal wear to their soles and heels. Do not hesitate to observe the contours of the feet and legs of the child's parents for evidence of a familial tendency in the problem.

One of the most difficult parts in the diagnosis of foot problems in children is to explain the symptoms in terms of the seemingly minor positive findings in many of the cases. So many children have equally severe or even more marked anatomic deviations without any symptoms that it is easy to dismiss many of these patients with the advice that "they will grow out of it." Perhaps many of them do spontaneously outgrow their troubles, but so many eventually turn up in clinics for crippled children or in the offices of pediatricians or orthopedists that one could wish the family doctor might see these children early and institute the simple measures which ultimately give relief.

Knock Knees

The majority of children brought to medical attention for genu valgus come for cosmetic reasons rather than because of any

symptoms of foot and leg strain. Those with symptoms will be apt to have pronated feet and valgus positioning of the heel. The latter group tends also to be of asthenic build, with relaxed joints generally, poor posture, abdominal ptosis and an appearance of fatigue and poor coordination. The complaint of the mother may be only that the child is clumsy, frequently stumbles, or seems to have no endurance. A history of being a finicky eater or of indefinite intake of vitamin D is frequent. Suggestive stigmas of rickets are not rare in this group. The amount of separation of the malleoli as the child stands with the knees just touching should be recorded, photographically if possible. If the separation is three or four fingerbreadths or more, particularly in the presence of pronated feet, the findings are likely to be the explanation of any symptoms of foot or leg strain.

Treatment will consist of shoe corrections as the major therapy, supplemented by postural exercises, vitamin supplements and daily supination exercises for the feet as needed. The mechanical problem is to alter the shoes in such a way that the knees are forced apart as the child bears weight on them. The shoes must be well constructed, have laces and carry a one-eighth to three-sixteenths inch wedge at the inner side of each heel. A heel which is extended forward along the inner margin of the shoe (Thomas heel) will increase the effectiveness of the wedging and transmit the correction more effectively to the feet and legs. These measures will usually relieve any symptoms of fatigue and foot strain very promptly but will require many months to alter the cosmetic appearance of knock knees. Parents must therefore be advised at the outset to procure shoe corrections on all of the child's shoes, under supervision, for several years at least.

Pronated Feet

Pronated feet (flatfoot) may be caused by several well recognized types of neurologic disturbances. Such feet are also commonly found in combination with other musculoskeletal deviations (genu valgus, torsion of the tibia, tight tendo achillis), including congenital fusions of the bones of the tarsus. They may or may not give rise to impaired function of the foot. A child with moderately severe flatfoot may be brought in because he walks with feet pointing out and wears off the medial aspects of his soles and heels. The next child with pronated feet may be doing his own "supination exercises" inside his shoes: curling the toes down and walking on the lateral aspects of his long arches. This will cause him to toe in as he walks—ding-toe gait. The leg with a slightly snug heel cord gains more apparent dorsiflexion for the foot by rolling in on the arch and throwing the forefoot into abduction at each step. Such a patient may appear to have flatfoot but in reality may have only a heel cord which needs stretching exercises. Such a situation can develop from prolonged bed rest for rheumatic fever or other childhood illnesses. A severe case of pes valgoplanus may be caused by congenital bony anomaly, paresis of the anterior and/or posterior tibial muscle, spasticity in the peroneal muscles, short tendo achillis, or secondary to neurologic deficit such as mild paraplegia associated with cerebral palsy. It may be the first symptom of a degenerative central nervous system illness.

Having made the necessary diagnostic studies, we devise the treatment according to the severity of the deformity. Untreated flatfoot will not improve by growth alone. Function in a position of deformity will cause the deformity to become more marked in a growing child. Regardless of the cause of the pronation, treatment must attain the neutral position during weight-bearing. This is most effective over a period of time if both passive devices and active exercises are used. The majority of children with simple pronation of the feet are able to form a perfectly normal appearing arch when they flex the toes and walk on the lateral borders of the feet ("walking like a cowboy"). Parents will occasionally state that the child has done that spontaneously at home. He has thus obtained relief from the ligamentous strain imposed by walking without using his muscles to help hold up the arch (a peg-leg type of gait or "flatfoot shuffle").

Treatment of pronated feet requires passive support of the arch while walking plus specific exercises to bring the child's muscles into the walking pattern, eventually to take over the job of holding the arch in proper contour. Shoe corrections alone will not convert a severely pronated foot into one with normal contours and function.

The most important part of the footwear is the shoe itself. It must be well made, fit well around the heel and the arch, have a firm shank (steel for severe cases), must lace, and should be made of leather rather than composition substitutes. The shoe must be able to reshape the foot, rather than vice versa. Support to the arch may be accomplished by "orthopedic shoes" with a built-in "cookie" under the arch, by separate rubber or felt arch inserts or by leather wedges along the medial aspect of the sole and heel as needed. The Thomas heel is very helpful. A combination of these methods is usual, depending on the foot and the stage of therapy.

Exercises should be kept simple, supervised by the parents daily and joined in by parents or others in the family where the patient is a younger child. The exercise of "walking like a cowboy" (already described) brings into full play the motor units which assist the ligamentous structures in support of the arch. The physician should supervise such a plan of therapy at regular but decreasing intervals as treatment progresses satisfactorily.

Shoes

The child or adult with "normal feet" requires primarily a shoe which will protect his feet from injury by the substances upon which he walks. Any shoe with a firm sole will qualify for this purpose. An infant who is not yet bearing weight needs only a shoe with cosmetic advantages, the usual "prewalker." A child who is standing but not yet walking may well profit by a high shoe which holds the foot in good weight-bearing alignment, with a firm sole. One sees fat babies who spend several months standing on deep crib mattresses with inadequate support for the ankles and who subsequently walk late and eventually seek help for pronated feet. Certainly the child who suffers from some type of foot problem requires a shoe which can transmit to the foot and leg such corrections as the physician may wish to prescribe. High shoes are better for this purpose than Oxfords. Shoes that lace are more effective than those with straps to the tarsus. If a corrective heel is being prescribed, its action is more effective on the foot and tarsal structures if the shank is firm or even rigid. If a single or double upright short brace is being used (for genu varus, genu valgus, drop foot, or talipes equinus), the shoe must have a steel shank to transmit the action of the brace to the entire foot, to prevent the foot from deforming the shoe.

The size of the shoe is of extreme importance in children with any significant foot problem. It is not rare to see a child with flatfoot wearing inside the shoe an arch support which rests beside the child's arch rather than underneath the arch because the shoe is too wide for the child's foot. Such a shoe will permit the laces to be drawn tightly together and yet leave loose wrinkles around the sides of the arch. Shoe salesmen are well versed in the advisability of leaving the toes unrestricted, but in so doing are apt to fit the child with high shoes which fit too loosely about the heel and tarsus. It is rare to find shoes fitted too small to a child, yet very common to find them fitted too large. Frequently the shoes are still too large when they are worn out, yet the clerk will advise a larger size to satisfy the parents' remarks about how fast the child is growing. Many parents prefer shoes slightly large because they are easier to put on the child's foot without opening the laces widely. If the child has a deformed foot or one with limited motion, he should be furnished a "surgical shoe" which laces clear to the toe, rather than shoes which are perpetually too large. Use of a fluoroscope in fitting shoes is to be viewed with caution because of the possibility of damaging young epiphyses from injudicious exposure. Clinical palpation of the forefoot, great toe, the break in the sole and the fit around the arch and at the heel gives much more useful information than the fluoroscope.

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Postgraduate Medicine

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WHEN HE COMES ASHORE

THE health and safety of their forces afloat has long been the concern of naval military leaders, who recognized that disease could play havoc with any fighting organization. As early as the end of the first century A.D. a medical unit was an integral part of the organization of every Roman warship. Over the succeeding centuries it was frequently noted that campaigns failed when shipboard disease ran rampant and could only succeed provided an effective number of the crew remained well and sound.

From its inception, the primary mission of the Medical Department of the United States Navy has been to keep the greatest possible number of personnel ready to sail the ships and man the guns. The result of the continued effort to reduce the incidence of disease and injury, aided by the phenomenal advance in medical science of the past 50 years, is evident in the statistics for Navy and Marine Corps personnel.

In 1900 the annual incidence rate for all diseases, injuries and poisonings was about 800 per 1000, with a mortality of 7.8. Five per 1000 of these deaths were caused by disease and 2.8 by injuries. At that time the leading cause of deaths from disease was typhoid fever, with drowning as the major killer in the injury group. By 1910 typhoid fever was coming under control and tuberculosis replaced it as the disease responsible for the most deaths among naval personnel.

With the advent of the automobile, a gradual shift occurred in deaths caused by injuries. By 1923 the effects of the gasoline age were beginning to be felt in the armed services, with 5 deaths caused by automobile accidents in that year among Navy and Marine Corps personnel. In 1930 the Frankenstein monster of the highways overtook and replaced drownings as the leading cause of accidental deaths, and each succeeding year has seen more and more of our deaths related to injury by motor vehicle.

Continued effort by the Medical Department and improvements in medical knowledge resulted by 1939 in reduction of the annual death rate from disease to 0.8 per 1000, with diseases of the circulatory system in the leading place. By contrast, the importance of injuries was accentuated by the fact that by this time 60 per cent of all deaths were attributable to accidents.

It has long been said that the Navy mother's prayer has been that God would protect her boy when he goes to sea. If the current situation were understood, however, her prayer today might well be that God would pro-

tect her boy when he comes ashore! In 1950 over twice as many Navy and Marine Corps deaths resulted from motor vehicle accidents as from all diseases combined, about 90 per cent of the accidents occurring while the victims were on leave or liberty.

Recently the Navy experienced a tragic accident when the U.S.S. Hobson was sunk during training maneuvers in the Atlantic. In that catastrophe, 176 lives were lost at one time. Even a major tragedy of such magnitude will, however, be overshadowed during 1952 by the number of persons, pleasure bound or going to or returning from home via automobile, who will never reach their destination. If the death rates pertaining to those who are killed in motor accidents while on leave or liberty remain constant between 1950 and 1952, there will be more lives lost in just three months of this year than were lost when the Hobson sank.

The medical officer is saving the lives of an increasing number of military personnel who would formerly have died from disease. At the same time our modern age of fast living is creating a monster that is taking their lives, most frequently in the prime of life. In one sense it would seem that lives are being saved with the right hand, only to be thrown away with the left. The remedy is that every driver be made to recognize his responsibility when he gets behind a wheel and to remember that safety on the highway can be attained only when it is practiced and not merely preached.

LAMONT PUGH
Rear Admiral, MC, U.S. Navy
Surgeon General of the Navy

THE USE OF VIRUS IN HUMAN CANCER

THE Sloan-Kettering Institute for Cancer Research presents an unusual progress report, concerned with the effects of inoculations of virus on cancer in experimental animals and in the human. The Institute is searching for a virus that will kill cancer, for a method that may control the multiplication of cancer-killing virus in the body and for some way of adapting virus so that it will destroy cancer cells without damaging normal cells. The viruses studied have included influenza A, herpes simplex and Russian spring-summer encephalitis viruses. The last named will kill cancer in animals but cannot be employed in humans because it causes general infection. In Siberian epidemics it has produced 40 per cent mortality. Thus far efforts to find a drug that would control the virus and all attempts to adapt the virus have been fruitless.

A number of viruses have been found which will destroy cancer in experimental animals. Uniformly they are neurotropic viruses. The viruses sometimes become noninfective for man. Sometimes they are deadly for mice and ineffective in man. Attempts are being made to develop virus particles that will grow in cancer cells without an injurious effect on other human tissues. Here is a crucial paragraph from the progress report:

> An effort was then made to find a virus strain which was allied to one which had shown cancer-destroying power in the animal, but which had recently been isolated from human beings and so could produce more regular infection. The field work of the National Foundation for Infantile Paralysis provided such an agent. In the course of a survey of natives in certain areas in Egypt, blood samples had been drawn from apparently well individuals and inoculated into mice. In one instance these animals developed symptoms. The virus recovered proved to be a fresh strain of one of the viruses which had been used in our experiments. This new virus strain, allied to our old strain West Nile, is known as Egypt 101.
>
> Egypt virus 101 has now been inoculated into 26 patients with cancer. In 19 cases there has been evidence of the multiplication of the virus with the production of mild, barely discernible symptoms . . . There has been in these studies, no evidence of injury to the central nervous system, unless a transient drowsiness and twitching for a few hours in 1 patient is to be considered the exception to the rule . . .
>
> Of the 19 patients in whom evidence of Egypt virus 101 infection could be established, there have been 4 instances in which substan-

tial diminution in size of the cancer tissue mass was effected. Two of these were patients with lymphosarcoma and 2 had cancer of the large intestine, a form of cancer which has never before responded even temporarily to any general chemotherapeutic measure. Other forms of cancer, such as melanoma and epidermoid cancers have been unaffected.

Further studies established that patients developed immunity to the virus after which cancer grew again rapidly. Examinations of biopsy material showed the cancer to be a mass of dead and dying cells with the persistence of a few living cells. These few remaining living cells eventually multiplied with great rapidity. The viruses were also able to damage the cells of metastases.

The progress report emphasizes that virus infection in man or animals is self-limiting. Antibodies are developed which are specific for the virus. The development of this immunity prevents the re-use, in the same patient, of a particular virus with potential cancer-destroying power. Effective treatment for cancer by the virus method requires development of an unrelated series of viruses, each one trained by long adaptation to destroy the particular type of cancer. Another complication is individual variation among people to virus infections and differences among cancer samples in susceptibility to viruses.

"There is as yet no proof," says the report, "that a curative virus for man can be developed—but only hope for such an outcome based upon the experiments here reviewed." Limited and transient effects in restraint of two forms of cancer in man have been achieved under experimental conditions by virus infections. The results are certainly not yet applicable to the treatment of patients. But the investigators anticipate intensification of the work on cancer-destroying viruses. Four research beds have been made available for the study of these effects in man. Ten beds will be devoted to the work in the near future. There is reason to hope that progress will be made and another progress report is looked for in the not too distant future.

MORRIS FISHBEIN

MORE TROUBLE WITH BRITISH NATIONAL HEALTH SERVICE

LATE in March a question was raised in the House of Lords in Great Britain on the cost of the National Health Service which has now reached 400,000,000 pounds annually. Viscount Buckmaster pointed out that there was apparently no upward limit on the operation of the health act. Last year four prescriptions had been written for every man and woman and child in England. The general practitioners have had an improvement in their remuneration but this does not seem to be a cure for the majority of the existing evils. The promised health centers have never materialized and general practitioners are gradually being excluded from hospitals, including even the cottage hospitals. Lord Shepherd pointed out that the answer to the problem might be in the establishment of a full-time staff of physicians. Many readers will remember that predictions were freely made that the present system would eventuate in a full-time, salaried medical staff.

In a symposium on health services held in London, April 22, Dr. Andrew Topping, dean of the London School of Hygiene and Tropical Medicine, prophesied that there would be a salaried medical service in 10 years. Lord Moran, who is physician to Winston Churchill, earnestly asked the House of Lords not to allow politics to enter into the health care of the people. He insisted that an increased tax on prescriptions and dental treatment would demolish the structure of the health service and was an instance of politics. Lord Moran said that the most deep-rooted cause of discontent among physicians was the insidious decline in the status of the general practitioner. Lord Moran said that "the clock could not be put back." Patients should not be persuaded to be treated at home but practitioners should be allowed to follow their patients into the hospital.

There are 500,000 beds in the hospitals of England of which only 6,449 are in general practitioner hospitals. Lord Moran said that "it was surely not right that 5,000 consultants

should work under ideal conditions while 20,000 practitioners were working under scientifically unsound conditions."

In his discussion of the fact that 50,000,000 pounds a year is spent on drugs, Lord Moran pointed out that according to the system that prevails in Denmark, lifesaving essential drugs are given free, desirable but not essential drugs are charged to the public at 40 per cent of their cost and the public pays 100 per cent for placebos. A similar plan has been in operation in Australia for 18 months. The representative of the government in his reply to the charges stated that neither the present government nor its predecessors were satisfied with the working of the 1946 act. He pointed out that a committee of the Central Health Services Council, under the chairmanship of Sir Henry Cohen, was considering the broader aspects of the organization of general practice. In an attempt to limit overprescribing, a booklet called "Prescribers' Notes" was being sent to doctors. This booklet is evidently designed to encourage physicians to prescribe remedies in the pharmacopeia rather than proprietary remedies.

The bill in the House of Commons which is designed to enable the government to put charges on certain services, including prescriptions, has had a stormy time. Many hours have been spent and hundreds of amendments have been offered to which the Labor Party makes such serious objections that after several weeks only the first nine lines of the amending act have been discussed.

The new Minister of Health, Mr. H. F. C. Crookshank, has said that the government found it necessary to put a charge on dentures and spectacles in order to keep the expenditures within a ceiling of 400,000,000 pounds. Summarizing the clauses of the new bill, Mr. Crookshank explained that the Labor government had taken power in 1949 to make a charge for medicines and appliances prescribed by general practitioners. The present bill extended this power to outpatients; inpatients would continue to get medicines and appliances free. The appliances affected include surgical boots, abdominal supports, elastic hosiery and wigs. The new charges placed on such appliances are expected to bring in 250,000 pounds per year. School children would not be charged for appliances. Two exemptions to dental charges will include children up to the age of 21 and expectant mothers. The government hoped that these charges would encourage more dentists to join the school dental service on a part-time basis.

Three members of the House of Commons discussed the statement by Mr. Crookshank and were against the changes in the measure that have been proposed. Dr. Edith Summerskill said that the drug bill was too high, representing one-eighth of the total expenditures under the act; it was never out of control before 1946. She felt that high-powered salesmen on behalf of the drug manufacturers were persuading doctors to prescribe expensive proprietary drugs for their more well-to-do patients. The approximate proportion of proprietary prescriptions under the National Health Insurance scheme before the war was 3 per cent, by 1947 had risen to 7 per cent, by 1948 to 12 per cent, by 1949 to 21 per cent, and today was over 30 per cent. Dr. Summerskill felt that savings should be made not on the pockets of the sick poor but out of the millions spent on expensive drugs for better-off people. She proposed that the minister revise the National Formulary more often and instruct pharmacists not to dispense proprietary drugs unless the doctor indicated that there was no equivalent in the National Formulary.

Mr. Aneurin Bevan said that the award of 40,000,000 pounds to general practitioners had shocked the majority of the people. He felt that it would destroy the whole system of the National Health Act; the general practitioners were entitled to an advance and if any funds were available for the improvement of the National Health Service, they had the first claim. However, he felt that the disparity now was too great and that it would create trouble throughout all of the industrial services. Mr. Bevan said that if money was to be saved, it should be done by putting dental treatment or drugs entirely outside the service but to have a service half in and half out would make in-

surmountable administrative difficulties. Mr. Bevan felt that the whole trouble lies in the fact that "the medical profession was ill-disciplined."

Mr. Iain MacLeod said that the ceiling of 400,000,000 pounds was irrational and that a new study ought to be made to determine the extent to which health should occupy the total national expenditure. He thought that charges would have a deterrent effect. The charge on dentures had a deterrent effect of about 50 per cent. Unfortunately the poor people suffer more than the well-to-do.

One member of the House of Commons argued that most of the increase in the drug bill was due to expensive new remedies rather than to proprietary drugs. Another said that the school dental service had always been inefficient and second-rate and that the only good dental service was being given to the children who were cared for by dentists in private practice.

These discussions are an indication of the extent to which the British National Health Service is causing unlimited amounts of trouble and debate. As a result of the tremendous time taken by the House of Commons to discuss the matter, what is now called the "guillotine" rule has been invoked and the House of Commons is to complete its considerations in short order. At the time of this writing the decisions have not yet been made.

MORRIS FISHBEIN

PHARMACOLOGY IN MEDICAL PROGRESS

THE first academic appointment in the field of pharmacology in the United States was that of J. J. Abel as professor at the University of Michigan in 1890. He was born in 1857 and he was for almost 40 years professor at Johns Hopkins. Contributions to pharmacology date far back in medical history. Therapeutics is no doubt the oldest of the branches of medical science. According to Castiglione the scientific study of the action of drugs was foreshadowed by Magendie's study of arrow poisons in 1809 which has been called the beginning of experimental pharmacology. Credit for initiation of the development of modern, scientific pharmacology is given to Rudolf Buchheim, professor at Dorpat and Giessen in Germany, who organized the first exclusively pharmacologic laboratory as an independent part of the study of physiology.

Professor O. Sidney Orth,[1] professor of pharmacology and anesthesiology, University of Wisconsin School of Medicine, now calls attention to the fact that the greatest decade of therapeutic advancement ever witnessed in medicine is just ending. This is the period of the sulfonamides and antibiotics, of the antihistaminics, synthetic analgesics, anticoagulants, muscle relaxants, pernicious anemia factors, corticosteroids and hormonal extracts. Professor Orth notes that the practitioner is already confronted with more drugs for use in treatment than anyone can manage to remember, yet still lacks drugs for many specific symptoms and ailments. Moreover, pharmacology is intimately bound with research in biochemistry, enzymology, oncology, bacteriology, physiology and pathology and subject to new technics derived from anatomy, chemistry and physics.

The purpose of a drug is to alter the action of a cell. While stimulating or helping one group of cells it may be injuring or inhibiting another group of cells. Its beneficial or harmful effects are definitely related to dosage used, solubility, speed and extent of absorption and elimination and many other factors. Determinations are made of the chemistry of the product, its rate of absorption, its toxicity, its dissemination to various cells and tissues, its place of action, the effects of single doses and of long continued administration, its concentration in the cells and its method of elimination. Animal tests lead to the eventually necessary human trials and to application in the clinic. The introduction of a new drug in modern medicine is a slow, painstaking and costly process.

MORRIS FISHBEIN

1. ORTH, O. SIDNEY: Pharmacology, an essential specialty in medical progress. Medical Horizons 2:1, 1952.

ELISE STRANG L'ESPERANCE

MEN OF *Medicine*

"For Significant Contributions to Medicine"

Although this department of POSTGRADUATE MEDICINE *is regularly headed "Men of Medicine," this month's biographic sketch is devoted to a "woman in medicine," whose contributions to medical practice and education have been truly outstanding. For these contributions and for her devotion to the highest ideals of her profession, the Editors are pleased to include Dr. Elise L'Esperance in the list of leading contemporary physicians honored in this series.*

SOME 268 pilot cancer detection clinics, scattered throughout the United States, testify to the unflagging zeal and the undaunted courage of one woman—Dr. Elise Strang L'Esperance. All of these clinics are outgrowths of the first permanent cancer detection facilities anywhere in the world which were founded by Dr. L'Esperance in 1937 in a little old building of the New York Infirmary for Women and Children in New York City.

Director and pathologist of the Infirmary laboratories since 1910, the pioneering physician had started a modest forerunner of the clinic in 1933. There she had been vastly impressed by the many young women who told her of their fears about cancer and their inability to find a place where their fears might be fully allayed.

Thus, when her mother and a sister died within three days of one another, the earnest pathologist decided to establish a clinic where the problems of such worried individuals might be solved. Feeling that the clinic would be a fitting memorial to her loved ones, the clinic idea was discussed with the remaining sister and devoted companion, May Strang. And Miss Strang agreed that the clinic would be a vital tribute. Both felt that a living enterprise would be far more suitable than the stained glass window to adorn a church edifice, which the sisters had previously considered. And so the Kate Depew Strang Cancer Detection Clinic came into being.

Physicians generally were not yet fully awake to the possibilities of periodic examinations to reduce the mounting cancer mortality figures. Even the late, great Dr. James Ewing failed to recognize the possibilities when plans for the new clinic were discussed with him.

The eminent pathologist had been Dr. L'Esperance's mentor. He had taught her that cancer develops slowly, that it often follows prolonged irritation, that there is a certain time interval before full malignancy. Dr. Ewing believed firmly that early diagnosis was highly important in the quiescent interval between the local disease and full-blown cancer. He knew full well that effective treatment must be instituted while the process is localized. More than 10 years earlier, he had stated that "in the control of cancer, prevention must play a prominent role for it appears more and more evident that early diagnosis alone is not capable of accomplishing the desired reduction in death rate."

On the other hand, Dr. Ewing was not impressed by the idea of a clinic where seemingly healthy persons would be checked for cancer. "It will cost a lot of money," he said, "and I don't think people will come to be examined."

But the determined woman said, "When patients come to us with cancer symptoms, it is apt to be too late. Let us go to them while there is yet time."

Realizing how much the clinic meant to his associate, Dr. Ewing finally advised her to go ahead. He said that he would watch from the

side lines and see what happened. It was wholly possible that she might be right. Prevention and early diagnosis through the periodic examination of healthy persons might, after all, be a practical part of a medical health service.

From the beginning of the clinic activities, Dr. L'Esperance stressed the need for *complete* physical examinations. She warred particularly against the all too common practice of limiting diagnostic search in women to the breast and pelvis. The physician believed this to be a hazardous practice apt to give a false sense of security. Anatomic structures other than those concerned with sex functions often proved to be the seat of cancerous growths.

The examinations as performed in the first Strang Clinic, like those performed today, included a complete survey of the skin surfaces, nasal and oral cavities, eyes, ears, blood pressure, height and weight. The chest was examined by percussion, auscultation and photo-roentgenographic or fluoroscopic methods. Palpation of the abdomen was followed by a pelvic examination that included vaginal and cervical Papanicolaou smears. Confirming surgical biopsies were performed on all suspicious lesions. A rectal examination, including a proctosigmoidoscopic examination, was conducted on all patients over 45 years of age. There were also a complete blood count, a urinalysis and a serologic test for lues. The entire procedure was repeated when the patient was re-examined. Those under 45 were urged to return annually and those over 45 were told to come back every six months.

Only 75 women came to the clinic that first year. But 150 came the next year and the numbers doubled those of the previous years on each of the two succeeding years.

The results impressed Dr. Ewing and he invited Dr. L'Esperance to start a similar clinic at Memorial Hospital. There he believed that the new cancer prevention and detection program would have even greater opportunities for growth. Just how far-reaching those opportunities would be was something that neither of the new clinic's enthusiastic founders could have foreseen.

Having invited Dr. L'Esperance to open and direct a clinic at Memorial Hospital, it was necessary to find space for the clinic. But space was at a premium in 1940 when the new facilities were made available to the public. As a result the patients found themselves wedged into a room about the size of a close-fitting telephone booth. To make matters worse, the clinic idea was soon expanded to include both men and women.

The director knew from the first that the space allotted was inadequate. There were too many serious-minded individuals ready and eager to avail themselves of the facilities which offered complete physical examinations. So the director began casting about for more space. With her usual direct and practical way of pushing aside difficulties, she made a room-to-room survey of the hospital to determine which rooms were used for only part of the day. As quickly as she located a room unoccupied for an afternoon or morning, she moved part of the clinic into that room.

Other physicians began to worry. "Whatever you do, don't tell L'Esperance that you use your room only part of the day," one told another. "If she finds out, the first thing you know the Strang Clinic will have your room and you'll be out."

Thus, as the patients returned time after time for their follow-up visits they were assigned first to one and then to another part of the great hospital. Shortly after it opened, Memorial Hospital's Strang Clinic had started to metastasize and soon made itself felt all over the institution.

Staff members sighed with relief when the Strang Clinic building was erected in 1946. Even the director was optimistic. Surely now, at long last, there would be plenty of room for the clinic. But within a few months, the clinic was handling patients at the rate of 30,000 a year and facilities threatened to become more crowded than before. By 1950, work as hard as Dr. L'Esperance and her associates might, there was a waiting list of 6000 men and women.

Altogether, the director and her associates had plenty of worries. Among other problems was the matter of how many hours the assist-

ing physicians should devote to clinic activities. Possessed of magnificent vitality which she lavished unstintingly upon her work, Dr. L'Esperance refused to tolerate anything short of complete dedication to clinic activities among her confreres. She had made great personal sacrifices so that the clinic might be a reality and she expected other physicians to face their tasks at Memorial Hospital in an altogether serious manner.

She was determined that nobody scheduled for any day be turned away without attention on that day. So there was a standing rule that no physician might leave the building until the last patient had received care. Physicians who cast desperate glances at the clock around 4:00 o'clock, or announced that come what may they had to make a living and snatched their hats always found an immovable woman between them and the door. And whatever their reactions may have been, they had to accept the inevitable and remain at the clinic. Their secretaries must explain as best they could to their patients waiting in private offices in various parts of the city.

While no longer actively engaged in the directorship of Strang Clinics, the influence of Dr. L'Esperance remains and the rules she laid down continue to guide all clinic activities. Through her persistent and sustained efforts, the clinics she founded offer services to the public. They also offer training for young physicians and continued, intensive research to facilitate the prevention and early diagnosis of cancer. The clinics founded by her are proving grounds for new procedures and her principle of mass-scale health screening and the education of well persons has reached out to point up the early manifestations of many disease conditions. This principle has been added to the curricula of medical schools to instruct the doctors of tomorrow and forms one of the truly notable contributions that will echo down the ages.

As viewed through the years, there is an interesting cleavage in the activities of Dr. L'Esperance. The earlier portion of her career was strongly influenced by the medical women she had known at the Woman's Medical College associated with the New York Infirmary. She had graduated at the college in 1899 and has never ceased to serve the ideals on which that institution was founded, even when the college ceased to exist except as a memory in the hearts of those who held it dear.

"The dignity, earnestness and courage of the women I knew there," says Dr. L'Esperance, "had a tremendous influence on an impressionable young woman. They taught me patience and a stubborn tenacity of purpose which is a valuable asset in any chosen field."

It was wholly fitting that Dr. L'Esperance should be the American woman selected as the recipient of the Elizabeth Blackwell Citation in 1949. The award commemorated the one hundredth anniversary of the graduation from the medical school of Geneva College of Elizabeth Blackwell, the first woman in America to receive an M.D. degree. The "10 outstanding women in the world," one from each of 10 countries, were selected by the authorities of Geneva College to be the recipients of the Citation upon this occasion. Dr. L'Esperance also received the Citation in 1950 given "for significant contributions to the practice and teaching of medicine."

This woman had early determined to follow in the footsteps of her father, the late Dr. Albert Strang, a much loved family physician with rare diagnostic ability. Thus young Elise Strang turned to the study of medicine at an age when most Westchester County girls of her social position were interested mainly in making good marriages and acquitting themselves properly in the social circles in which they moved.

Following graduation she interned at famed Babies Hospital under the eminent Dr. Emmett Holt. There followed a brief and not too happy period in private practice as a pediatrician.

Dr. L'Esperance approached private practice as she did everything. She was filled with boundless enthusiasm and found no task too irksome. But she became increasingly distressed by a realization of inadequacy—her own inadequacy and that of physicians generally. There was so much that doctors did not know. Soon her hunger for more knowledge became more acute than her desire to

continue in private practice. So she locked the door of her office and never returned.

The rest of her professional career was to be devoted to medical research and to furthering the education of physicians generally. Having the courage of her convictions and the vitality to stick with them wherever they led, she threw herself unreservedly into the new projects. First, there were research activities in the field of tuberculosis. Important contributions of that period are preserved in several papers published in collaboration with Dr. William A. Park. At that time, Dr. L'Esperance was a member of the Tuberculosis Research Commission of the New York City Research Laboratories.

Other papers followed. Among the more notable were the reports on studies of the Wassermann reaction published jointly with Dr. Arthur F. Coca and the reports of her research studies in gynecologic pathology and in Hodgkin's disease.

The second and most important portion of Dr. L'Esperance's career began in 1910 when she became an assistant to Dr. James Ewing in the department of pathology at the Cornell University School of Medicine. It was under him that the groundwork was laid for her later contributions.

Two years after joining Dr. Ewing, she was made an instructor in his department. She was also the recipient of the Mary Putnam Jacobi Fellowship which included six months of study in Munich. But the study period abroad was interrupted by the first World War and she returned to this country and completed her graduate studies at Cornell University. In 1920, she was named assistant professor in the department of pathology, the first woman in the history of Cornell University to attain that rank. Dr. L'Esperance now holds the title of clinical professor of preventive medicine at Cornell University Medical Center.

Numerous posts have come to this woman whose achievements have helped to set aside old notions about the position of women in a professional world. In 1919, she became instructor in clinical pathology for the Second Surgical Division of Bellevue Hospital. Later, she was named assistant pathologist to both The New York Hospital and Memorial Hospital and pathologist to Harlem Hospital and Manhattan Maternity Hospital.

Dr. L'Esperance has served as president of the Women's Medical Society of New York State. Other honors and awards include the Clement Cleveland Award of the New York City Cancer Committee, given for outstanding achievements in cancer education for the year 1948. She received the Friendship Award for Eminent Achievement from the American Women's Medical Association in 1946 and the following year was the recipient of the Cancer Award in Medical Research incident with the Exposition of Women's Arts and Industries. In 1950, Dr. L'Esperance received the Lasker Award of the American Public Health Association, one of four scientists so honored.

The Lasker Award Statuette is a gold replica of the classical Winged Victory of Samothrace and symbolizes victory over death and disease. The statuette which, together with $1000 and a leather-bound citation illuminated in Middle Ages style, constitutes the Lasker Award is regarded among the nation's primary medical honors.

A conversation with Dr. L'Esperance is an experience to be remembered. A handsome, auburn-haired individual, she makes her presence felt even on a brief meeting. And her energy, vigorous intellectual approach, humor and generosity pour themselves out to those around her. At the same time, she somehow manages to convey the impression that she is particularly interested in the person with whom she is conversing at the moment. Altogether, it is easy to recognize her reputed powers as a natural leader who draws loyalty from those with whom she works.

"The future rests with us all," says Dr. L'Esperance. "Each generation must contribute its share to our progress."

Surely such words come with nothing short of prophetic wisdom from a woman whose contributions for the future have been so great.

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants.

• TREATMENT OF INGUINAL WOUND

Question: On June 22, 1951, the patient fell with considerable force on a broken shovel handle which entered the right thigh about 3 inches below the inguinal ligament. As near as can be determined, the handle penetrated about 6 inches, apparently through the obturator foramen. The wound was debrided and closed with a drain and the patient was given considerable amounts of penicillin.

The wound drained for about one week and healed well. Pain and tenderness in the right lower quadrant ensued about a week later and there was spiking of the temperature. The patient was hospitalized on July 2, 1951, and found to have a large retroperitoneal hematoma palpable on the medial surface of the right ilium. This subsided without incident within two weeks, at which time he was discharged from the hospital.

About September 1, 1951, the right groin became tender and swollen, and in about three or four days the area broke down and began draining a heavy, purulent exudate. He was given oral sulfonamides and parenteral penicillin at first, then CHLOROMYCETIN® and terramycin, later, local instillation of varidase. In spite of these, the exudate continued, although it became more serous in character. Culture of the exudate on September 29 showed *Proteus mirabilis* or *P. rettgeri*, these being most sensitive to chloromycetin and terramycin.

On December 27, 1951, the patient was taken to surgery and the right inguinal area was examined. A sinus tract was found which admitted a No. 12 catheter about 8 to 9 inches. This was left *in situ* and injected with IODOCHLOROL® and an x-ray study was made. This showed the catheter to follow a course posteriorly and retroperitoneally to the wing of the right sacrum.

On December 28 an unsuccessful attempt was made to pass a catheter into the right ureter. Indigo carmine injection came through normally but the catheter could not be passed because of the acute angle of the ureterovesicular orifice and intramural portion of the ureter. Intravenous urogram was normal on this date except for a narrowing of the right ureter adjacent to the catheter in the fistulous tract.

Exploratory laparotomy on December 28 showed the catheter to run retroperitoneally through the base of the pelvis and to come up through the reflection of the anterior surface of the sacrum and terminate at the edge of the sacrum at the pelvic inlet, immediately adjacent to the right ureter, which was thickened throughout its course. There was no pelvic mass.

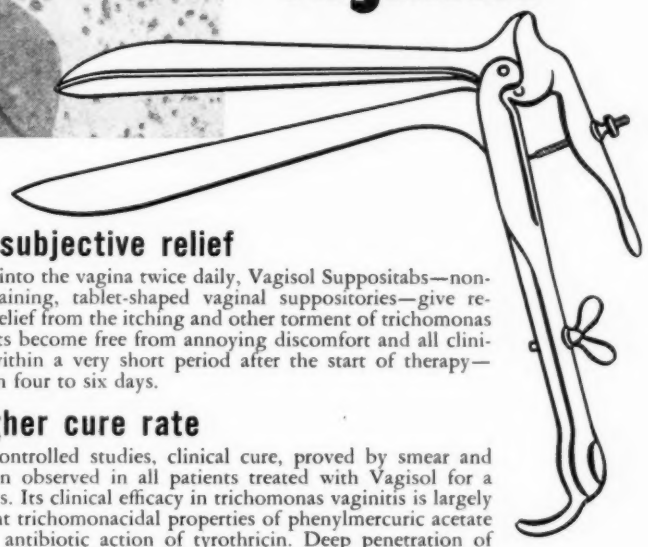
Lavage with intravenous AUREOMYCIN® solution was carried out daily (through the catheter) until the patient was discharged from the hospital on January 5, 1952. A repeat intravenous urogram on February 25 revealed nothing further. Culture of the exudate on March 18 showed *Aerobacter cloacae* and this was found to be moderately sensitive to aureomycin, terramycin and neomycin. The inguinal wound has continued to drain to date.

I would appreciate any suggestions you may be able to offer toward clearing up this resistant condition.

M.D.—California

(Continued on page A-28)

in trichomonas vaginitis



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ANSWER: Provide free drainage of the involved area, even if it means wide incision. Thoroughly curet all tracts, especially any extensions that may have escaped detection to date. Be certain that there is no elusive foreign body, osteomyelitis or communication with the ureter that has precluded control of the infection.

• SUDDEN ONSET OF FAINTING AND VOMITING

Question: A 55 year old married housewife first became ill two months ago when she awoke at 1:00 A.M. with a headache in the right temporal region. Prior to that time she had enjoyed good health—in fact, she had not consulted a physician for 21 years. Following the headache she began vomiting, but there was no nausea. Between episodes of vomiting there were fainting spells. At times these would occur daily, and at other times they would occur every three or four days, sometimes every week. They were noted more frequently during her menstrual periods.

Physical examination was negative. Blood pressure was normal. There were no beating radial arteries. Biopsy of the cervix was negative for malignancy. Her blood count was practically normal. Repeated urinalyses were negative. Blood sedimentation test was negative and her basal metabolic rate was normal. Values for uric acid, blood urea, nonprotein nitrogen and creatinine were all normal. An electrocardiogram suggested some left heart strain—hypertension (?).

At present the fainting spells occur less frequently than before, but the patient complains of a tired feeling in the abdomen. Her menstrual periods occur every three weeks and last for five days, the flow being excessive for the first two days. There is dysmenorrhea. She has had four pregnancies, and in the last one the labor was difficult.

Any suggestions you may have will be greatly appreciated.

M.D.—Michigan

This inquiry was submitted to consultants in neurology and in gynecology for reply.

ANSWER: The sudden onset of pain in the temporal region associated with vomiting and fainting suggests the possibility of aneurysm of the circle of Willis. The persistent fainting spells may be an indication of carotid sinus syndrome. For symptomatic treatment, atropine is recommended up to the level of tolerance (uncomfortably dry mouth and pulse rate of 120) with further investigation of the patient by carotid angiography.

WALTER FREEMAN

ANSWER: The episodes of headache and vomiting probably are not related to the menstrual function, although it is unusual for a woman aged 55 years not to have cessation of menses. I assume the negative physical examination included a complete pelvic examination. I would suggest a radiogram of the cranium and examination of the ocular fundi. Had she been under unusual nervous strain?

ROBERT D. MUSSEY

• BILATERAL CRYPTORCHISM IN NEWBORN INFANT

Question: A newborn infant has bilateral cryptorchism, with the testes, I think, in the inguinal canal. I would like to know the treatment for this, i.e., whether surgery is indicated and, if so, when would be the optimum age.

M.D.—Ontario

ANSWER: Bilateral cryptorchism is not uncommon in the newborn infant. Descent of the testes frequently occurs spontaneously in the early years. If it has not taken place by the beginning of puberty, a series of injections of chorionic gonadotrophins may be done. If this is not effective, surgical treatment should then be undertaken. The subject is very well discussed in R. H. Williams' "Text Book of Endocrinology," chapter 5.

• REDUCTION OF FEHLING'S SOLUTION

Question: Can normal urine give a false positive test with Fehling's solution if it is boiled for 20 minutes?

M.D.—Illinois

ANSWER: There are a number of substances in urine other than sugar which will reduce Fehling's solution. Some of these appear in "normal" urine. Long boiling (20 minutes) increases the tendency for the reduction of the solutions.

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► UROLOGICAL PATHOLOGY

By Peter A. Herbut, M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Two volumes. 1,222 pages and complete index in both volumes; 527 illustrations, 2 in color. 1952, Lea & Febiger, Philadelphia. $24.00.

Most features of a textbook of urology are here combined with a much more detailed and better illustrated presentation of urologic pathology than can be included even in a large textbook of urology. The material is arranged according to organs, a system which leads to some duplication of data but which the author chose deliberately in the interests of convenient arrangement.

The first chapter in the book reviews the embryology of the urinary tract and of the male genital system. There is a brief discussion of the structure and function of the organ concerned in each chapter. A definite outline is followed in the presentation of each abnormality, disease, and disorder: definition, age distribution, cause, clinical manifestations, gross and microscopic appearance, complications, clinicopathologic correlation, diagnosis (largely clinical), treatment (in outline) and prognosis. Urography is omitted. In the case of neoplasms modes of spread are reviewed, and in those disorders which influence the output and character of hormones (as with the adrenal gland) pathologic physiology is discussed in considerable detail.

One can always find something to criticize. Your reviewer's chief objection is focused upon the author's apparent approval of "the growing tendency" among pathologists to drop the term "papilloma of the bladder" in favor of "papillary carcinoma of a low grade of malignancy," and to leave the final decision as to the character of the lesion to the cystoscopist "who, after all, has the advantage of having seen the gross lesion." To me this represents a disavowal of responsibility by the pathologist either from the suspicion that the histologic examination is of only tentative value or from fear of being wrong. It seems to me that the function of the pathologist in making an examination of a stained section is to render an independent opinion based on the evidence at his disposal. This must of course include data from the clinician. If he fails to do so by calling all epithelial neoplasms of the bladder malignant, the histologic examination loses much of its value, and one might as well throw biopsy of tumors of the bladder out of the window. It seems to me that the pathologist ought to say that, from the microscopic sections and clinical data, this is a papilloma or a carcinoma. If he is forced to take the middle ground he can ask for another specimen to study. To call them all carcinomas is to confuse completely all attempts to evaluate the results of treatment by creating a fundamental difference between those clinics with papillomas and those without, and the situation is sufficiently confused without that.

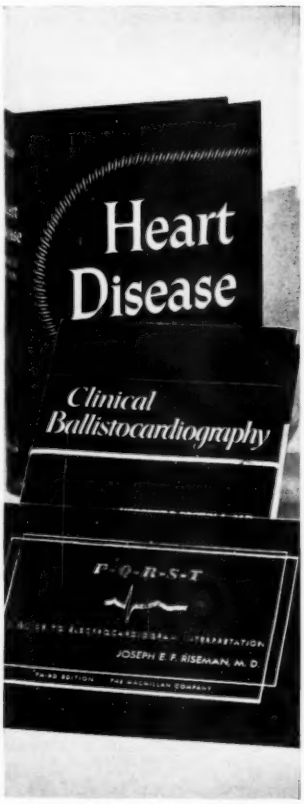
This work should be of real value both to those practitioners and medical students who wish to understand better the occasional lesion of the urinary or male genital tract, and to those (residents in and practitioners of urology) who wish to improve their understanding of urologic pathology and to use the book as a starting point for reviewing the literature for publication.

It seems to me that these volumes would be improved if most of the clinical material were omitted and if more space were devoted to pure pathology, particularly of the unusual lesions.

C. D. C.

(Continued on page A-52)

3 New publications on diagnosis and treatment of circulatory disorders



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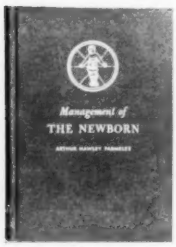
► MANAGEMENT OF THE NEWBORN

By Arthur Hawley Parmelee, M.D., University of Southern California School of Medicine, Los Angeles. 358 pages, illustrated. 1952, The Year Book Publishers, Inc., Chicago. $7.00.



Although only 6 per cent of all newborn infants are premature, about 50 per cent of premature infants die. Adequate prenatal care is the answer to this problem. Because of the preventable hazards at and immediately following birth, the physician who sees the child at this time shares the responsibility to help reduce the unnecessary high mortality rates during the first week of life.

This book is written in the tradition of the clinician of a generation ago. Without benefit of elaborate apparatus but chiefly by the use of his five senses, the author has accumulated a mine of clinical information.

This is not a textbook in the usual sense. It is rather a vivid and fascinating story of the newborn; why he is what he is, what his peculiar problems are and what preventive and curative care is required under all circumstances. To the author the newborn is not just a "byproduct of pregnancy and labor" but a human being in his own right.

In a chapter on the characteristics of the normal newborn, the author outlines a method of evaluating the health status of the newborn which gives many clues in the search for the abnormal. The chapter on the management of the premature will give the practicing physician all the necessary information to treat the newborn adequately.

Dr. Parmelee devotes four chapters to the pathologic disturbances of the newborn. The first is on disturbances directly due to birth processes, such as fractures, dislocations, trauma of the skin, peripheral nerve injuries, intracranial accidents and asphyxia, atelectasis and other interferences with respiration.

The next chapter is on disturbances due to abnormal variations of physiologic peculiarities, such as hemorrhagic diseases of the newborn, icterus, initial weight loss, tetany and adrenal insufficiency. Next comes a chapter on disturbances due to prenatal factors, such as acute infectious diseases of the mother, syphilis, maternal metabolic and systemic diseases and the most common congenital malformations, and last is a section on disturbances due to acquired infections and other postnatal hazards, such as acute infections of the skin, umbilicus, ears, mouth, nose and throat and respiratory tract and epidemic diarrhea and septicemia.

M. S.

► SURGERY AND THE ENDOCRINE SYSTEM

By James D. Hardy, M.D., University of Tennessee Medical College. 153 pages with 43 figures. 1952, W. B. Saunders Company, Philadelphia & London. $5.00.

Some of the most significant recent advances in surgery have been in the field of the endocrine system. In this new book the author presents the surgical aspects of endocrine gland diseases in a concise and clear manner so that the reader should be able to grasp the fundamental concepts involved and their clinical application in everyday practice.

The first six chapters are of particular interest since there is complete integration of the newer concepts which have been evolved in the last decade which serves to add new knowledge to the old surgical problems. The alarm reaction in the surgical patient is discussed in detail together with the role of the adrenal glands in this phenomenon. Methods of diagnosis of adrenal insufficiency preoperatively and postoperatively are given. The role of the endocrine glands in the all-important problem of fluid regulation and shock is graphically represented and explained in detail with charts and graphs.

The second half of the book is a rather straightforward presentation of the surgical aspect of the individual glands. The anatomy, embryology, pathology, clinical considerations, preoperative and postoperative care and the surgical treatment are described. Numerous drawings illustrate surgical technics.

The author has drawn freely from the current literature and the views of the authorities in the field are discussed. A complete bibliography accompanies each chapter.

Y. S.

(Continued on page A-54)

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1. *Seley, S. A.: Am. J. Dig. Dis. 13:238 (July) 1946.* 2. *Rossien, A. X.: Rev. of Gastroenterol. 16:34-52 (Jan.) 1949.* 3. *Rossien, A. X. and Victor, A. W.: Am. J. Dig. Dis. 14:226-229 (July) 1947.* 4. *Batterman, R. C. and Ehrenfeld, I.: Gastroenterol. 9:141 (August) 1947.*

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► OFFICE ENDOCRINOLOGY

By Robert B. Greenblatt, M.D., Professor of Endocrinology, Medical College of Georgia, Augusta. Ed. 4. 545 pages with 276 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $10.50.

Doctor Greenblatt's earlier lectures and clinics have been thoroughly revised for this volume. Great care is taken by the author and the publishers to point out that this book is *not* intended to be a textbook. The author has devoted himself to the clinical diagnosis and treatment of conditions with which he is familiar. Laboratory procedures are completely described, and the evaluation of these procedures is well discussed. Because of the limitations imposed upon the author by the nature of this volume, some oversimplifications have been necessary in this section. His conservative attitude toward laboratory tests tends to counteract any shortcomings due to brevity.

The excellent sections on gynecologic endocrinology reflect the major interests of the author. Doctor Greenblatt expresses here a long experience with careful clinical and laboratory investigation and the endocrine therapy of disorders of female reproductive endocrinology, and does so with a remarkable balance of brevity and perspective. The recent use of cortisone and corticotropin in endocrine and nonendocrine conditions is well outlined, and Selye's theory of adaptation is presented briefly and critically.

Particularly to be recommended are Doctor Greenblatt's sections dealing with the difficult clinical problem of hirsutism in the female. One might wish that he had paid equal attention to the clinical features of acromegaly. The statement that the diagnosis is usually made on sight can, of course, be applied only to the advanced case. More details of the clinical signs and symptoms, and particularly to those symptoms of acromegaly which simulate the symptoms of hyperthyroidism, would be most welcome. The photographs of the hands of acromegalic women would be more striking if contrasted with pictures of a normal female hand.

The author has an engaging colloquial style and a dry humor, never obtrusive, which enlivens the more theoretical discussions. Quotations from the classics are apt and well chosen. The sections on diagnostic procedures in themselves will make the volume valuable.

G. S. G.

► LIVER INJURY

Transactions of the Ninth Conference, April 27-28, 1950, New York City. Edited by F. W. Hoffbauer, M.D., Department of Medicine, University of Minnesota Medical School, Minneapolis. 232 pages, illustrated. Sponsored by the Josiah Macy, Jr. Foundation, New York. $3.00.

From the report of the conference covered by this book, it is possible to enjoy *in absentia* the interchange of ideas and integration of clinical experiences shared by leading investigators in the field of study. Included are discussions of recent correlation of hepatic function and structure based on liver biopsy studies, the question of the reason for specific changes in the particular function test involved, the problem of liver dysfunction, such as the cause of hepatic coma, and the appearance of pigment in livers of healthy persons.

Another section is devoted to the clinical aspects of hepatic vascular physiology. Studies of normal subjects, as well as cases of cirrhosis and hepatectomy, are considered. An important contribution is the review on the study of hepatic lymphatics, and convincing proof of the permeability of the intrahepatic biliary tract in regurgitation jaundice is presented. Pioneer work on the experimental production of dietary cirrhosis, with formation of fatty liver, fatty cysts and intravascular fat with embolic phenomenon, is demonstrated. The intriguing disease of Kwashiorkor is poignantly portrayed by J. P. Davies of Uganda, East Africa. It is stated that the pathology of the disease is chiefly an atrophy of the enzyme-secreting cells, especially in the pancreas and small intestine. Low protein intake is incriminated as a causal factor.

The book concludes with a report on the timely topic of lipotropic agents, vitamin B_{12} and folic acid. Vitamin B_{12} is shown to have a lipotropic activity and thus its importance in therapy is enhanced.

R. J. W.

(Continued on page A-56)

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► CALCULATION OF INDUSTRIAL DISABILITIES OF THE EXTREMITIES

By Carl O. Rice, M.D., Clinical Associate Professor of Surgery, University of Minnesota Medical School, Minneapolis. 289 pages with 204 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $10.50.

One of the most perplexing problems that the practicing physician encounters is the accurate rating of an industrial disability. Most methods used heretofore require considerable study and keen observation of disabling conditions over an extended period. The busy practitioner who is called on occasionally to rate a disability has long been desirous of a simple, accurate method of determination that would closely approach the findings of the more experienced surgeons. Such a volume is now available. Considering that most disabilities of the extremities are directly related to the loss of function, the author has based his concept on the amount of retained motion computed against the normal arc of movement. Aware that certain intangible features remain difficult to evaluate, or at least to measure accurately, it is implied that the consideration of useful retained motion will engross these indefinite factors. Further, it becomes relatively simple to measure the degree of motion and compare these results with the normal range. The amount of disability therefore is directly related to the measurable loss of useful activity in the extremity. This appears to be a new basis for the estimation of physical incapacities produced by industrial trauma.

Other authors do not agree with this opinion but rather feel that various factors such as quickness of action, coordination, strength, security, endurance, etc. should not be overlooked. However, in comparing the results obtained, it becomes apparent that the computation of loss of motion will define a similar percentage of disability.

The monograph includes historic and anatomic considerations, relative value of the various units and fundamental principles in the calculation of a disability, and concludes with chapters on the actual calculation of disability in the upper and lower extremities. H. O'P.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

The Story of the Adaptation Syndrome. By Hans Selye, M.D., Professor and Director of the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 225 pages, illustrated. 1952, Acta, Inc., Montreal. $4.50.

Survey of Clinical Pediatrics. By Lawrence B. Slobody, M.D., New York Medical College, Flower and Fifth Avenue Hospitals, Metropolitan Hospital, and Children's Center, New York City. 471 pages. 1952, McGraw-Hill Book Company, Inc., New York, Toronto and London. $7.50.

Clinical Ballistocardiography. By Herbert R. Brown, Jr., M.D., Vincent deLalla, Jr., M.D., Marvin A. Epstein, M.D. and Marvin J. Hoffman, M.D., University of Rochester School of Medicine and Dentistry, Rochester, New York. 188 pages, illustrated. 1952, The Macmillan Company, New York. $5.50.

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